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Synthesis of diverse β-quaternary ketones via palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enones

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Abstract

The development and optimization of a palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enone conjugate acceptors is described. These reactions employ air-stable and readily-available reagents in an operationally simple and robust transformation that yields β-quaternary ketones in high yields and enantioselectivities. Notably, the reaction itself is highly tolerant of atmospheric oxygen and moisture and therefore does not require the use of dry or deoxygenated solvents, specially purified reagents, or an inert atmosphere. The ring size and β-substituent of the enone are highly variable, and a wide variety of β-quaternary ketones can be synthesized. More recently, the use of NH_4PF_6 has further expanded the substrate scope to include heteroatom-containing arylboronic acids and β-acyl enone substrates.

Keywords

Conjugate addition; Palladium; Asymmetric catalysis; Quaternary center; Enone; Boronic acid

1. Introduction

Synthesis of all-carbon quaternary stereocenters by means of asymmetric catalysis remains a challenging problem in synthetic chemistry.[1] Historically, the 1,4 addition of a nucleophile to a suitable α,β-unsaturated conjugate acceptor has been a reliable means of synthesizing these challenging quaternary stereocenters.[2] Many groups have pioneered methods for this transformation employing highly reactive organometallic reagents (e.g., diorganozinc,[3] triorganoaluminum, [4] and organomagnesium reagents[5]) to react with a large array of electrophiles under copper catalysis. Rigorously anhydrous conditions are a requirement of these approaches, as they uniformly utilize water-sensitive reagents. As an alternative, Hayashi developed chiral rhodium complexes that successfully catalyze the asymmetric conjugate addition of various organoboron reagents to conjugate acceptors in very high

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yields and enantioselectivities. [6,7] More recently, the rhodium system has been expanded to include syntheses of quaternary stereocenters.[8] In particular, the development of chiral diene ligands has facilitated the rhodium-catalyzed conjugate addition of sodium tetraaryl borates (Ar_4BNa) and arylboroxines $(ArBO)_3$ to enones to afford products containing all-carbon quaternary stereocenters.[9,10] However, it should be noted that these reactions cannot use common and commercially available arylboronic acids.[9-11]

Upon undertaking studies to develop a palladium-catalyzed asymmetric conjugate addition capable of synthesizing quaternary stereocenters, we noted that there were only examples of asymmetric synthesis of *tertiary* stereocenters in the palladium literature.[12] Concurrent with our early studies, Lu and co-workers reported that the dicationic complex $[(bpy)Pd(OH)]_2{\cdot}2BF_4$ was capable of catalyzing the conjugate addition of arylboronic acids to 3-methylcyclohexenone to synthesize racemic products featuring quaternary stereocenters.[13] In 2011, we reported the discovery of an asymmetric palladium-catalyzed conjugate addition based on a catalyst derived in situ from $Pd(OCOCF_3)_2$ and a chiral pyridinooxazoline (PyOx) ligand.[14] These reactions were demonstrated on a broad spectrum of arylboronic acid and enone substrates, and were found to be remarkably tolerant of both oxygen and water. Subsequently, we disclosed the use of NH_4PF_6 and water as synergistic additives to accelerate the rate of the reaction. Fortuitously, these additives also allowed reactions to be conducted at temperatures as low as ambient temperature.[15]

Herein, we discuss report a full account of the development of these reactions and discuss the full scope of the chemistry to date.

2. Development and optimization of reaction conditions

2.1. Identification of chemically competent ligand and reaction conditions

To achieve the desired enantioselective conjugate addition, the reaction of 3-methylcyclohexen-2-one (**1**) with phenylboronic acid (**2**) was investigated in the presence of various palladium catalysts and chiral ligands (Table 1). We hypothesized dinitrogen ligands that were less sterically bulky than large arylphosphine ligands would successfully synthesize the highly congested quaternary stereocenter of β-disubstituted ketone **3**, and were pleased to find that bipyridine (bpy, **4**) enabled full conversion of enone **1** when treated with palladium(II) acetate and phenylboronic acid in protic solvents. Unfortunately, a number of other standard ligand scaffolds failed to afford any conversion to the desired conjugate addition product under identical reaction conditions. Sparteine (**6**), PyBox (**7**), and a variety of bis-oxazoline (**9** and **10**) and phosphinooxazoline (**8**) did not enable the transformation. 'Ligand-free' conditions (**5**) also failed to provide any product. Notably, pyridine (**11**, 12 mol %, 2 equiv) failed to deliver any product, insinuating that architectural features of the bidentate bpy scaffold enabled the desired reaction.

Success with bpy and lack of success with chiral bis-oxazoline ligands led us to propose that a C_1 symmetry chiral ligand based on the bpy scaffold would be a suitable catalyst. The presence of a pyridine ring was required, however the small bite angle and five-membered metallocycle chelate seemed equally important. We reasoned that modification of one pyridine moiety of bpy would allow for the introduction of a chiral group (Fig. 1, hypothetical ligand **12**), while still maintaining the five-membered chelate and narrow bite-angle. We quickly discovered that substituted pyridinooxazoline ligands (**13**)[14] provided high levels of enantioselection.

Identification of a functioning chiral ligand ((*S*)-*t*-BuPyOx, **14**) prompted us to consider the effects of solvent on the yield and enantioselectivity of the reaction. A preliminary solvent screen led us to observe that polar, coordinating solvents hindered the reaction (Table 2, entries 1–3). Moving toward non-polar solvents, such as toluene (entry 4), encouraged higher conversions and modest enantioinduction, however, heating these reactions (entries 6 and 7) failed to drive the reactions to full conversion. Fortuitously, dichloromethane (entry 5) provided 87% isolated yield of the desired conjugate addition adduct in 91% ee.

To further optimize the reaction, we next looked at the effect of different palladium sources. The use of palladium(II) halides afforded no reaction (Table 3, entries 1 and 2). The reactivity could be rescued via halogen abstraction upon treatment with AgOTf (entry 3), however, this reaction produced ketone **3** in low enantioselectivity. In the presence of ligand **14**, palladium(II) carboxylate sources were capable of catalyzing the desired reaction (entries 4 and 5). The acetate counterion (entry 4) led to modest chemical yields of the desired conjugate addition adduct in 93% ee. A catalyst derived from palladium(II) trifluoroacetate and pyridinooxazoline **14** produced the desired ketone product **3**[16] in 87% yield and 91% ee (entry 5).[17] By using 1,2-dichloroethane in place of dichloromethane as solvent, and increasing the reaction temperature from 40 to 60 °C, ketone **3** was isolated in 99% yield and 93% ee (entry 6). The high yield and enantioselectivity were maintained even upon addition of 10 equiv of water (entry 7). Furthermore, the amount of phenylboronic acid was reduced to 1.1 equiv with no detrimental effects (entry 8).

A final examination of solvent and palladium sources was undertaken following the disclosure of a highly enantioselective palladium-catalyzed conjugate addition by Minnaard and coworkers whereby a dicationic palladium catalyst is generated in MeOH.[18] However, we found that highly polar solvents failed to produce product (Table 4, entries 2 and 3). Switching to dicationic palladium by employing tetrakis acetonitrile palladium(II) tetrafluoroborate facilitated no conversion in methanol at a variety of temperatures (entries 4–6), or as a mixture with dichloroethane as cosolvent (entry 6). Finally, we failed to generate a catalyst in situ from isolated (PyOx)$PdCl_2$ by treatment with sodium hexafluorophosphate (entry 7).

2.2. Identification of chemically competent ligand and solvent conditions

Having successfully optimized the reaction conditions, we next examined the reaction with other members of the PyOx or related quinolinooxazoline (QuinOx) ligand series (Table 5, **17** and **18**). Ligands with electron-donating (**15**) or electron-withdrawing (**16**) substituents on the pyridine moiety both furnished the product in high yield, but with decreased enantioselectivity. Next, employing QuinOx ligands **17** or **18** resulted in a dramatic decrease in both the reactivity and enantioselectivity, presumably due to poor chelation of palladium due to the increased steric bulk adjacent to the pyridine nitrogen. Modifying the chiral substituent to groups other than *tert*-butyl also led to decreased enantioselectivity, as we observed PyOx ligands bearing isobutyl (**20**), phenyl (**21**), or isopropyl (**22**) substitution to deliver ketone **3** in quantitative yield, but significantly depressed ee. Similarly, PyOx ligands without substitution at the 4-position (**19**) afford no appreciable enantiocontrol and deliver ketone **3** nearly as a racemic mixture.

Following the discovery that the addition of NH_4PF_6 and water accelerate the reaction (see Section 3 for discussion), we reexamined a large number of chiral and achiral ligands to determine if the new conditions facilitated an expanded class of ligands to successfully catalyze the reaction. Unfortunately, all phosphine ligands we tried failed to achieve appreciable conversion (Table 6, **23, 24**, and **25**). The drop in conversion from dppe (**24**) to dppbz (**25**) led us to question whether ligand rigidity was detrimental to conversion. However, the nearly identical results observed with bpy (**4**), phenanthroline (**26**), and bathophenanthroline (**27**) suggest that rigidity of the ligand scaffold has minimal effect on conversion.

We screened a number of chiral diamine ligands under the newly optimized conditions as well. The best conversion was observed with a bis-oxazoline with a bite angle similar to that of bpy (Table 6, **34**), followed by proline-derived **32**, which also features a five-membered metallocycle chelate. Ligands forming six-membered metallocycles (**28** and **29**) performed poorly, however those containing *gem*-dimethyl (**31**) or cyclopropyl (**35**) substituted bridging methylene groups showed improved conversion. We believe this to be the result of the quaternary center on the ligand backbone enforcing a smaller bite angle. Additionally, sparteine (**6**), PHOX (**33**), and PyBox (**30**) ligands delivered no conversion to the desired product.

3. Determination of substrate scope

To determine the substrate scope, a wide variety of arylboronic acids were exposed to the optimized reaction conditions (Table 7). Generally, *para*-substituted arylboronic acids react with good yields and enantioselectivities. Alkyl substituted products (red colored, Table 7) are generally formed in good yield and ee, such as those formed by 4-methyl- and 4-ethylphenylboronic acids (**36** and **37**). However, arylboronic acids bearing substituents with greater electron-donating capacity, such as 4-benzyloxyphenylboronic acid or 4-methoxyphenylboronic acid react to form products with diminished yields and enantioselectivities (**38** and **39**). A wide range of functional groups can be utilized successfully. Even a silyl ether is tolerated (e.g., **44**), however in modest yield. Arylboronic acids bearing electron-withdrawing substituents (blue colored) tend to perform extremely well. Both 4-acylpheny- and 4-trifluoromethylphenylboronic acids react with quantitative yield and 96% ee to form ketones **40** and **41**. The product of 4- chlorophenylboronic acid (**42**) is formed in 94% yield and 95% ee, and the product of 4-fluorophenylboronic acid (**43**) is afforded in 92% ee. Finally, *meta*-substitution on the arylboronic acid also furnishes products in high ee and yield. 3-Methylphenylboronic acid and 3-carbomethoxyphenyboronic acid both afford product ketones (**45** and **46**, respectively) in greater than 90% ee (Table 8).

More recently, we discovered that the addition of NH^4PF^6 and water accelerate the reaction, and allow for lower temperatures to be employed.[15] Typically, reactions under these conditions occur between room temperature and 40 °C. Gratifyingly, we discovered that these milder conditions facilitate increased yields with substrates that had reacted with good ee, but poor yields under the initial reported conditions (in the absence of NH_4PF_6 and water). In some cases, the isolated yield nearly doubled. For example, reaction of 3-chlorophenylboronic acid saw a yield increase from 55% to 96% yield. Likewise, the product formed from 3-bromophenylboronic acid (**47b**) increased from 44% yield to 84% yield. Even 3-nitrophenylboronic acid saw an increase from 40% to 81% yield. Furthermore, 2-fluorophenylboronic acid reacted with 70% yield and 77% ee under the newly modified conditions. In each of these cases, the increase in yield is met with effectively no change in ee.

Next, we tested a variety of β-substituted enones to examine the scope of the enone reactant (Table 9). A wide variety of alkyl substituted products can be formed, such as ethyl (**48**), *n*-butyl (**49**), and benzyl (**50**) substituents at the β-position, all which were afforded in greater than 90% ee. Furthermore, branched, bulky alkyl substituents could be successfully utilized, forming products such as isopropyl (**51**), cyclopropyl (**52**), and cyclohexyl (**53**). Heteroatom linkers (e.g., **54**) are suitable β-substituents as well. Finally, products formed from five- and seven-membered enones (**55** and **56**, respectively) were reacted with greater than 90% ee.

4. Plausible catalytic cycle

Computational and experimental work by our group in collaboration with the Houk laboratory suggests that the reaction is catalyzed by a palladium(II) cationic species (Fig. 2, **57**).[15a] We propose that the active catalyst is likely a palladium(II) hydroxide, which are known to undergo rapid transmetallation with arylboronic acids.[19] Though the precise role of NH_4PF_6 has not been established, we postulate that the presence of the non-coordinating counterion may stabilize the cationic intermediates on the proposed catalytic cycle, or otherwise favor a resting state, that is, on the productive catalytic cycle. This would have the effect of increasing the relative concentration of the active catalyst species, leading to the observed rate increase. Rapid reaction of palladium hydroxide **57** with arylboronic acid then affords cationic arylpalladium(II) **58**. Ligand substitution and substrate coordination, likely through the oxygen of the enone to form complex **60**, lead to insertion of the aryl-palladium bond when coordination via the enone olefin occurs (**59**). This olefin insertion is the enantioselectivity- determining step. The lowest energy diastereomer of this insertion reaction has been calculated to be transition state **59-ts**,[15a] which leads to the observed (*R*) stereochemistry of the product ketones. Migratory insertion of the substrate olefin into the aryl-palladium bond affords carbon-bound palladium enolate **62**, which likely isomerizes to its oxygen-bound tautomer, enolate **61**. Hydrolysis of this latent cationic palladium enolate (**61**) affords the product ketone (**3**) and regenerates the catalyst (**57**).

5. Expanded substrate scope

The discovery that reaction rates were dramatically increased by the addition of hexafluorophosphate salts and additional water represented an opportunity to expand the substrate scope. The additives promote successful reaction at 40 °C or lower, and thus substantially facilitate the reaction of substrates with temperature-sensitive functionalities (such as silyl ethers), or groups that may react with trace palladium(0), that is, formed by off-cycle pathways (such as aryl bromides).We next turned our attention to two other substrate classes: (1) β-acyl cyclic enones and (2) arylboronic acids containing nitrogen and other heteroatoms.

We considered that our β-arylation reaction constituted a synthetically useful means of synthesizing asymmetric 1,4-dicarbonyl compounds. Beginning with β-acyl cyclic enones (**63**), we were able to react a variety of arylboronic acids to synthesize asymmetric 1,4-dicarbonyl compounds (Table 10, **64a–g**). Interestingly, only products from the olefin insertion that form quaternary stereocenters were observed. The isomeric addition product, which would contain vicinal tertiary stereocenters, was not observed in any of the crude reaction mixtures by NMR spectroscopy.

Next, we strived to demonstrate that the reaction was tolerant of heteroatom substitution on the arylboronic acid. We proposed that aniline-derived boronic acids could be reacted when protected with electron-withdrawing functional groups. Cbz-protected aniline boronic acid **65a** reacted with modest yield (Table 11), but a promising 76% ee. Modification to the pivaloyl protected boronic acid **65b**, facilitated higher yields, but had minimal effect on enantioselectivity. Finally, trifluoroacetyl-protected **65c** afforded clean conversion to afford 98% of the conjugate addition adduct **66c** in 89% ee. The trifluoroacetyl group facilitated the reaction on a number of aniline-derived arylboronic acids, including methoxyphenyl trifluoroacetamide **65d**, trisubstituted acetamide **65e**, and 3-trifluoroacetamides **65f** and **65g**. Their successful reactions demonstrate the broad utility of these substrates.

6. Challenging substrates

Despite the many substrates that undergo facile conjugate addition, a number of substrates proved incompatible with the newly developed methodology (Table 12). Pyridine **67** presumably coordinates palladium and inhibits the catalyst, yielding no conjugate addition product. Allyl enone **68** also did not react, nor did enyneone **69**. β-Aromatic enones also failed, such as thiophene **70** and chloroarene **71**. Each of these substrates has functionality that can potentially interact with palladium; such interactions are likely detrimental to the catalyst.

Some arylboronic acids also proved to be poor nucleophiles. *ortho*-Substituted arylboronic acids were generally poor substrates; 2-chlorophenylboronic acid (Table 13, **73**) yielded only 2% of its corresponding product in 37% ee, while 2-methylphenylboronic acid (**74**) yielded 13% product in 22% ee. Arylboronic acids with reactive groups, such as iodide **76** and furan **77**, were not successfully employed in conjugate addition chemistry. Cyanophenylboronic acid **80** also failed to react. In general, heterocycles are not well tolerated, as observed by the lack of reactivity of indole **81**. Steric crowding of the reactive boronic acid site by the Boc protecting group may play a role in the poor reactivity. Likewise, the very electron poor fluoroarene **78** does not react, though steric congestion likely contributes to its poor performance as well. Interestingly, styrene moieties **79** and **82** also did not undergo addition. Additionally, it should be noted that electron-rich arylboronic acids (e.g., dimethoxyphenylboronic acid (**75**)) undergo rapid homocoupling and proteodeborylation under the reaction conditions. Thus, it is difficult to achieve synthetically useful yields of these electron-rich adducts. Furthermore, the enantioselectivity seems to be lower for these electron-rich arylboronic acids.

7. Conclusion and outlook

In summary, we have developed a widely applicable method for the synthesis of β-quaternary ketones of a variety of ring sizes utilizing a palladium-catalyzed, asymmetric conjugate addition of arylboronic acids to enone electrophiles. A wide array of arylboronic acids and enones were successfully employed in this transformation. Critically, the reactions are compatible with protic co-solvents, such as water, and display remarkable tolerance to atmospheric oxygen. Furthermore, the optimized ligand, (*S*)-*t*-BuPyOx (**14**), is easily synthesized and readily prepared on multigram quantities.[20] These features, in combination with the ease of handling of arylboronic acids, result in an operationally simple reaction with a straightforward procedure. All reactions described herein were performed in screw-top vials and without purification or distillation of any reagents or solvents. Application of this reaction method toward the catalytic asymmetric total synthesis of several natural product classes and the development of an asymmetric conjugate addition of heteroaryl substrates are currently underway in our laboratory.

8. Experimental section

8.1. Materials and methods

Unless otherwise stated, reactions were performed with no extra precautions taken to exclude air or moisture. Commercially available reagents were used as received from Sigma–Aldrich unless otherwise stated. Enone substrates (Table 3) were purchased from Sigma–Aldrich (3-methylcyclohexenone, 2-cyclohexene-1-one, chromone) or were prepared according to literature procedure.[21] Pyridinooxazoline ligands were synthesized according to literature procedures.[22] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OJ column (4.6 mm×25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm and flow rate of 1 mL/min, unless otherwise stated. Analytical chiral SFC was performed with a JASCO 2000 series instrument utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm×25 cm), or a Chiralpak IC column (4.6 mm× 10 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 210 or 254 nm and flow rates of 3 mL/min or 5 mL/min, as indicated below. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 125 MHz, respectively) and a Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{1}H NMR spectra are referenced to the centerline of $CDCl_3$ (δ 7.26) as the internal standard and are reported in terms of chemical shift relative to Me_4Si (δ 0.00). Data for ^{13}C NMR spectra are referenced to the centerline of $CDCl_3$ (δ 77.0) and are reported in terms of chemical shift relative to Me_4Si (δ 0.00). Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MultiMode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

8.2. Experimental procedures

8.2.1. (S)-4-(tert-Butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole (14)—The ligand was prepared according to literature procedures.[14,23] All characterization data match previously reported data.

8.3. Representative general procedure for the enantioselective 1,4-addition of arylboronic acids to β-substituted cyclic enones

A screw-top 1 dram vial was charged with a stir bar, $Pd(O\text{-}COCF_3)_2$ (4.2 mg, 0.0125 mmol, 5 mol %), (*S*)-*t*-BuPyOx (3.1 mg, 0.015 mmol, 6 mol %), and $PhB(OH)_2$ (61 mg, 0.50 mmol, 2.0 equiv). The solids were dissolved in dichloroethane (0.5 mL) and 3-methyl-2-cyclohexenone (29 μL, 0.25 mmol) was added. The walls of the vial were rinsed with an additional portion of dichloroethane (0.5 mL). The vial was capped with a Teflon/silicone septum and stirred at 60 °C in an oil bath for 12 h. Upon complete consumption of the starting material (monitored by TLC, 4:1 hexanes/EtOAc, *p*-anisaldehyde stain) the reaction was purified directly by column chromatography (5:1 hexanes/EtOAc) to afford a clear colorless oil (47 mg, 99% yield).

8.4. General procedure for the synthesis of racemic products

Racemic products were synthesized in a manner analogous to the general procedure using bipyridine (2.1 mg, 0.015 mmol, 6 mol %) as an achiral ligand.

8.5. Spectroscopic data for enantioenriched β,β-disubstituted cyclic ketones

8.5.1. (R)-3-Phenyl-3-methylcyclohexanone (3)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (93% yield). $[\alpha]_{D}^{25} - 56.1$ (*c* 1.36, $CHCl_3$, 92% ee). All characterization data match previously reported data.[9a,9b,4k,4f,4i,4c,13]

8.5.2. (R)-3-(4-Methylphenyl)-3-methylcyclohexanone (36)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (99% yield). $[\alpha]_{D}^{25} - 60.9$ (*c* 1.11, CH_2Cl_2, 87% ee). All characterization data match previously reported data.[9a,4i,k]

8.5.3. (R)-3-(4-Ethylphenyl)-3-methylcyclohexanone (37)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (90% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (ddd, *J*=2.0, 8.5 Hz, 2H), 7.16 (ddd, *J*=2.0, 8.5 Hz, 2H), 2.87 (d, *J*=14.0 Hz, 1H), 2.62 (q, *J*=7.5, 2H), 2.42 (d, J=14.0 Hz, 1H), 2.35–2.26 (m, 2H), 2.20–2.15 (m, 1H),1.93–1.83 (m, 2H),1.73–1.64 (m, 1H),1.31 (s, 3H), 1.23 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 144.7, 142.0, 127.9, 125.5, 53.2, 42.5, 40.8, 38.0, 29.8, 28.2, 22.0, 15.4; IR (Neat Film, NaCl): 2957, 2933, 2863, 1710, 1513, 1453, 1416, 1315, 1288, 1226, 1078 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1587, found 217.1592; $[\alpha]_D^{25} - 56.8$ (*c* 1.61, $CHCl_3$, 85% ee).

8.5.4. (R)-3-(4-Benzyloxylphenyl)-3-methylcyclohexanone (38)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (ddd, J=1.5, 2.0, 7.5 Hz, 2H), 7.39 (ddd, J=1.0, 7.0, 7.5, 2H), 7.33 (tt, J=1.5, 7.0 Hz, 1H), 7.22 (ddd, J=2.0, 3.5, 10.0 Hz, 2H), 6.93 (ddd, J=2.0, 3.5, 10.0 Hz, 2H), 5.04 (s, 2H), 2.85 (d, J=14.0 Hz, 1H), 2.42 (d, J=14.0 Hz, 1H), 2.30 (t, J=7.0 Hz, 2H), 2.18–2.13 (m, 1H), 1.92–1.83 (m, 2H), 1.71–1.62 (m, 1H), 1.30 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 157.0, 139.7, 137.0, 128.6, 127.9, 127.5, 126.7, 114.7, 70.0, 53.3, 42.3, 40.8, 38.0, 30.0, 22.0; IR (Neat Film, NaCl) 3066, 3027, 2947, 2873, 1710, 1609, 1579, 1510, 1453, 1426, 1379, 1312, 1290, 1246, 1181, 1021 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1673; $[\alpha]_D^{25} - 26.8$ (*c* 4.90, $CHCl_3$, 74% ee).

8.5.5. (R)-3-(4-Methoxyphenyl)-3-methylcyclohexanone (39)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 90:10) as colorless oil (58% yield). $[\alpha]_D^{25} - 47.9$ (*c* 1.05, $CHCl_3$, 69% ee). All characterization data match previously reported data.[9b,4k,f,c,i]

8.5.6. (R)-3-(4-Acetylphenyl)-3-methylcyclohexanone (40)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2/EtOAc=100:0 to 98:2) to afford colorless oil (99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (ddd, J=2.0, 9.0 Hz, 2H), 7.42 (ddd, J=2.0, 9.0 Hz, 2H), 2.90 (d, J=14.0 Hz, 1H), 2.58 (s, 3H), 2.47 (d, J=14.0 Hz, 1H), 2.38–2.26 (m, 2H), 2.25–2.20 (m, 1H), 1.98–1.88 (m, 2H), 1.68–1.59 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 197.6, 152.9, 135.2, 128.6, 125.9, 52.8, 43.2, 40.7, 37.8, 29.7, 26.5, 22.0; IR (Neat Film, NaCl) 2957, 2868, 1708, 1683, 1607, 1569, 1456, 1421, 1404, 1359, 1312, 1268, 1228, 1194 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{19}O$ $[M+H]^+$: 231.1379, found 231.1380; $[\alpha]_D^{25} - 58.9$ (*c* 1.39, $CHCl_3$, 96% ee).

8.5.7. (R)-3-(4-Trifluoromethylphenyl)-3-methylcyclohexanone (41)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (99% yield). $[\alpha]_D^{25} - 58.5$ (*c* 0.92, $CHCl_3$, 96% ee). All characterization data match previously reported data.[4k,f,i]

8.5.8. (R)-3-(4-Chlorophenyl)-3-methylcyclohexanone (42)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to

95:5) to afford a white solid (94% yield). $[\alpha]_{D}^{25} - 69.4$ (*c* 0.56, $CHCl_3$, 95% ee). All characterization data match previously reported data.[9b]

8.5.9. (R)-3-(4-Fluorophenyl)-3-methylcyclohexanone (43)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (84% yield). $[\alpha]_{D}^{25} - 59.5$ (*c* 1.00, $CHCl_3$, 92% ee). All characterization data match previously reported data.[9a,b]

8.5.10. (R)-3-(4-tert-Butyldimethylsiloxylphenyl)-3-methylcyclohexanone (44)— Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (ddd, *J*=2.0, 3.0, 9.0 Hz, 2H), 6.71 (ddd, *J*=2.0, 3.0, 9.0 Hz, 2H), 2.83 (d, *J*=14.0 Hz, 1H), 2.40 (d, *J*=14.0 Hz, 1H), 2.30 (t, *J*=7.0 Hz, 2H), 2.16–2.10 (m, 1H), 1.90–1.81 (m, 2H), 1.70–1.61 (m, 1H), 1.29 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 153.8, 140.1, 126.5, 119.8, 53.3, 42.3, 40.8, 38.1, 29.9, 25.6, 22.0, 18.1, −4.4; IR (Neat Film, NaCl) 2952, 2933, 2858, 1713, 1607, 1510, 1473, 1458, 1263, 1181 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{19}H_{31}O_2Si$ $[M+H]^+$: 319.2088, found 319.2090; $[\alpha]_{D}^{25} - 36.4$ (*c* 1.11, $CHCl_3$, 82% ee).

8.5.11. (R)-3-Methyl-3-(m-tolyl)cyclohexanone (45)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (99% yield). $[\alpha]_{D}^{25} - 59.8$ (*c* 2.95, CH_2Cl_2, 91% ee). All characterization data match previously reported data.[9a,4k,f]

8.5.12. (R)-3-(3-Methoxycarbonylphenyl)-3-methylcyclohexanone (46)— Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2/EtOAc 100:0 to 98:2) to afford a white solid (91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J*=1.5, 2.0 Hz, 1H), 7.88 (dd, *J*=1.5, 9.0 Hz, 1H), 7.51 (dd, *J*=2.0, 9.0 Hz, 1H), 7.39 (dd, *J*=9.0 Hz, 1H), 3.91 (s, 3H), 2.88 (d, *J*=14.0 Hz, 1H), 2.47 (d, *J*=14.0 Hz, 1H), 2.37–2.28 (m, 2H), 2.24–2.19 (m, 1H), 1.98–1.86 (m, 2H), 1.73–1.65 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 167.1, 147.9, 130.4, 130.2, 128.6, 127.5, 126.7, 53.0, 52.1, 42.8, 40.7, 37.7, 29.3, 22.0; IR (Neat Film, NaCl) 2952, 2878, 1720, 1604, 1582, 1438, 1350, 1310, 1273, 1243, 1209, 1194, 1120, 1085 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found 247.1334; $[\alpha]_{D}^{25} - 58.9$ (*c* 1.39, $CHCl_3$, 95% ee).

8.5.13. (R)-3-(3-Chlorophenyl)-3-methylcyclohexanone (47a)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (55% yield). $[\alpha]_{D}^{25} - 56.7$ (*c* 1.48, $CHCl_3$, 96% ee). All characterization data match previously reported data.[9a,b]

8.5.14. (R)-3-(3-Bromophenyl)-3-methylcyclohexanone (47b)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (44% yield). $[\alpha]_{\mathrm{D}}^{25} - 56.7$ (c 0.68, $CHCl_3$, 85% ee). All characterization data match previously reported data.[4i]

8.5.15. (R)-3-(3-Nitrophenyl)-3-methylcyclohexanone (47c)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (40% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (t, J=2.0 Hz, 1H), 8.08 (ddd, J=1.0, 2.0, 8.0 Hz, 1H), 7.66 (ddd, J=1.0, 2.0, 8.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 2.88 (d, J=14.0 Hz, 1H), 2.53 (ddd, J=1.0, 1.5, 14.0 Hz, 1H), 2.41–2.31 (m, 2H), 2.26–2.20 (m, 1H), 2.03–1.90 (m, 2H), 1.74–1.66 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 149.7, 148.6, 131.9, 129.5, 121.4, 120.7, 52.8, 43.1, 40.6, 37.6, 29.4, 22.0; IR (Neat Film, NaCl) 2957, 2873, 1713, 1525, 1480, 1453, 1426, 1347, 1298, 1226, 1107, 1075 cm^{-1}; HRMS (MultiMode ESI/APCI) m/z calcd for $C_{13}H_{15}O_3N$ [M]: 233.1052, found 233.1055; $[\alpha]_{\mathrm{D}}^{25} - 61.5$ (c 0.96, $CHCl_3$, 92% ee).

8.5.16. (R)-3-(2-Fluorophenyl)-3-methylcyclohexanone (47d)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (32% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2H), 7.07 (ddd, J=1.5, 2.0, 7.5 Hz, 2H), 7.39 (ddd, J=1.0, 7.0, 7.5 Hz, 2H), 7.33 (tt, J=1.5, 7.0 Hz, 1H), 7.22 (ddd, J=1.5, 7.5 Hz, 1H), 7.02 (ddd, J=1.5, 8.0, 13.0 Hz, 1H), 2.94 (d, J=14.5 Hz, 1H), 2.44 (d, J=14.5 Hz, 1H), 2.48–2.44 (m, 1H), 2.37–2.28 (m, 2H),1.96–1.87 (m, 2H), 1.67–1.60 (m, 1H), 1.41 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 128.3, 128.0, 127.9, 124.1, 116.7, 53.2, 42.4, 40.9, 35.7, 27.1; IR (Neat Film, NaCl) 2957, 2933, 2873, 1710, 1611, 1577, 1488, 1443, 1315, 1290, 1214, 1117, 1083 cm^{-1}; HRMS (MultiMode ESI/APCI) m/z calcd for $C_{13}H_{16}OF$ $[M+H]^+$: 207.1180, found 207.1188; $[\alpha]_{\mathrm{D}}^{25} - 41.0$ (c 0.64, $CHCl_3$, 77% ee).

8.5.17. (R)-3-Phenyl-3-ethylcyclohexanone (48)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (96% yield). $[\alpha]_{\mathrm{D}}^{25} - 74.5$ (c 3.39, $CHCl_3$, 92% ee). All characterization data match previously reported data.[4c,i,k,9a]

8.5.18. (R)-3-Phenyl-3-n-butylcyclohexanone (49)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford colorless oil (95% yield). $[\alpha]_{\mathrm{D}}^{25} - 56.7$ (c 1.48, $CHCl_3$, 91% ee). All characterization data match previously reported data.[4c]

8.5.19. (R)-3-Benzyl-3-phenylcyclohexanone (50)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (74% yield). $[\alpha]_{\mathrm{D}}^{25} + 01.0$($c$ 3.83, $CHCl_3$, 91% ee). All characterization data match previously reported data.[13]

8.5.20. (R)-3-Phenyl-3-iso-propylcyclohexanone (51)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (86% yield). $[\alpha]_{\mathrm{D}}^{25} - 79.4$ (*c* 3.24, $CHCl_3$, 79% ee). All characterization data match previously reported data.[13]

8.5.21. (R)-3-Phenyl-3-cyclopropylcyclohexanone (52)—Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (68% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.28 (m, 4H), 7.21–7.17 (m, 1H), 2.90 (dt, *J*=2.0, 14.5 Hz, 1H), 2.48 (d, *J*=14.5 Hz, 1H), 2.31–2.19 (m, 3H), 1.94–1.86 (m, 2H), 1.60–1.51 (m, 1H), 0.99 (tt, *J*=5.5, 8.5, 1H), 0.45–0.39 (m, 1H), 0.35–0.29 (m, 1H), 0.24–0.19 (m, 1H), 0.17–0.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 143.2, 127.6, 126.5, 125.7, 50.0, 44.9, 40.3, 34.1, 23.1, 20.8, 1.1, 0.0; IR (Neat Film, NaCl) 3081, 3057, 3007, 2947, 2873, 1708, 1498, 1443, 1421, 1315, 1285, 1226, 1046, 1023 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{19}O$ $[M+H]^+$: 215.1430, found 215.1425; $[\alpha]_{\mathrm{D}}^{25} - 83.1$ (*c* 1.39, $CHCl_3$, 88% ee).

8.5.22. (R)-3-Phenyl-3-cyclohexylcyclohexanone (53)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (86% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (ddd, *J*=2.0, 7.0, 8.0 Hz, 2H), 7.23 (ddd, *J*=1.0, 2.0, 8.0 Hz, 2H), 7.18 (tt, *J*=1.0, 7.0 Hz, 1H), 2.97 (dd, *J*=2.0,15.0 Hz,1H), 2.46 (d, *J*=15.0 Hz,1H), 2.26–2.17 (m, 3H), 2.07 (ddd, *J*=3.5, 12.5, 13.5 Hz, 1H), 1.94–1.88 (m, 1H), 1.84–1.75 (m, 2H), 1.68–1.56 (m, 2H), 1.52–1.45 (m, 1H), 1.44–1.38 (m, 1H), 1.37–1.31 (m, 1H), 1.26–1.17 (m, 1H), 1.11–0.95 (m, 2H), 0.88–0.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 143.8, 128.1, 127.4, 125.9, 49.5, 49.0, 47.2, 41.0, 33.6, 27.5, 27.4, 26.9, 26.5, 21.4; IR (Neat Film, NaCl) 2928, 2853, 1713, 1495, 1443, 1315, 1285, 1228 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{18}H_{24}O$ $[M+H]^+$: 257.1900, found 257.1888; $[\alpha]_{\mathrm{D}}^{25} - 52.4$ (*c* 3.87, $CHCl_3$, 85% ee).

8.5.23. (S)-3-(3-(Benzyloxy)propyl)-3-phenylcyclohexanone (54)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (65% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 7.27–7.24 (m, 5H), 7.18 (tt, *J*=1.5, 7.0 Hz, 1H), 4.37 (s, 2H), 3.30 (dt, *J*=1.5, 6.5 Hz, 2H), 2.93 (d, *J*=14.5 Hz, 1H), 2.43 (d, *J*=14.5 Hz, 1H), 2.33–2.26 (m, 2H), 2.22–2.16 (m, 1H), 1.98 (ddd, *J*=3.0, 10.0, 13.5 Hz, 1H), 1.86–1.77 (m, 2H), 1.68 (ddd, *J*=4.5, 12.0 Hz, 1H), 1.61–1.53 (m, 1H), 1.43–1.32 (m, 1H), 1.23–1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2, 144.8, 138.4, 128.5, 128.3, 127.6, 127.5, 126.4, 126.2, 72.7, 70.4, 51.0, 45.9, 41.0, 39.7, 36.6, 23.9, 21.4; IR (Neat Film, NaCl) 3057, 3027, 2947, 2858, 1710, 1602, 1495, 1451, 1359, 1312, 1280, 1228, 1100, 1075, 1026 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{22}H_{26}O_2$ $[M+H]^+$: 323.2006, found 323.1993; $[\alpha]_{\mathrm{D}}^{25} - 42.9$ (*c* 4.25, $CHCl_3$, 91% ee).

8.5.24. (R)-3-Phenyl-3-methylcyclopentanone (55)—Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (84% yield). $[\alpha]_{\mathrm{D}}^{25} + 21.3$ (*c* 1.51, $CHCl_3$, 91% ee). All characterization data match previously reported data.[4f,i,k]

8.5.25. (R)-3-Phenyl-3-methylcycloheptanone (56)—This product was synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc=100:0 to 95:5) to afford a colorless oil (85% yield). $[\alpha]_{\mathrm{D}}^{25}-75.1$ (*c* 1.34, $CHCl_3$, 93% ee). All characterization data match previously reported data.[4i,k,9a]

8.6. General procedure for the synthesis of 3-acetyl-3-aryl cyclic ketones

8.6.1. (S)-3-Acetyl-3-phenylcyclopentanone (64e)—A screw-top 1 dram vial was charged with a stir bar, $Pd(OCOCF_3)_2$ (3.4 mg, 0.01 mmol, 5 mol %), (*S*)-*t*-BuPyOx (2.5 mg, 0.012 mmol, 6 mol %), and $PhB(OH)_2$ (48 mg, 0.40 mmol, 2.0 equiv). The solids were suspended in dichloroethane (1 mL) and stirred at ambient temperature for 5 min, at which time a yellow color was observed. 3-Acetylcyclopent-2-enone (25 mg, 0.20 mmol, 1 equiv) and water (50 µL, 10 equiv) were added and the vial was capped with a Teflon/silicone septum and stirred at 60 °C in a heat block for 12 h. Upon complete consumption of the starting material (monitored by TLC, 20% acetone/hexanes, *p*-anisaldehyde stain) the reaction was purified directly by column chromatography (eluent gradient: 10% acetone/hexanes to 20% acetone/hexanes) to afford a clear colorless oil (29 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.24 (m, 5H), 3.13 (ddd, *J*=18.0, 1.7, 0.7 Hz, 1H), 2.77–2.69 (m,1H), 2.53 (dt, *J*=17.9, 0.8 Hz,1H), 2.47–2.37 (m,1H), 2.32 (dddd, *J*=8.5, 6.8, 4.1, 0.9 Hz, 2H), 1.97 (d, *J*=0.6 Hz, 3H); ^{13}CNMR(125 MHz, $CDCl_3$) δ 214.9, 207.7,140.7, 129.2, 127.7, 126.5, 61.2, 47.1, 36.5, 30.8, 25.4; IR (Neat Film, NaCl): 3059, 3026,1745,1705,159,1495,1446,1407,1355,1203,1151 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{13}H_{15}O_2$ [M+H]$^+$: 203.1072, found 203.1066; $[\alpha]_{\mathrm{D}}^{25}100.8$ (*c* 1.5, $CHCl_3$, 93% ee).

8.6.2. (R)-3-(4-Chloropheny)-3-acetylcyc lohexanone (64a)—Synthesized according to the general procedure, 0.25 mmol scale. The title compound was isolated as an off-white solid (53 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.18 (m, 2H), 2.85 (dt, *J*=1.4, 14.8 Hz, 1H), 2.63 (dt, *J*=1.1, 14.8 Hz, 1H), 2.48–2.20 (m, 4H), 1.87 (s, 3H), 1.80–1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 208.3, 208.1, 139.3, 133.8, 129.5, 127.8, 59.6, 48.6, 40.3, 31.5, 25.3, 21.1; FTIR (Neat Film, NaCl) 3397, 2951, 2875,1708,1490,1455,1420, 1402, 1356, 1319, 1235, 1183, 1140, 1097, 1012, 970, 829, 717 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{14}H_{15}ClO_2$ [M+H]$^+$: 251.0833, found: 251.0829; $[\alpha]_{\mathrm{D}}^{25}-6.74$ (*c* 3.2, $CHCl_3$, 96% ee).

8.6.3. (S)-3-Acetyl-3-(4-fluorophenyl)cyclohexanone (64b)—Synthesized according to the general procedure, 0.22 mmol scale. Title compound isolated as a pale yellow oil (45 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.19 (m, 2H), 7.11–7.03 (m, 2H), 2.87 (dt, *J*=14.8, 1.5 Hz, 1H), 2.65 (dt, *J*=14.8, 1.3 Hz, 1H), 2.38–2.34 (m, 2H), 2.32–2.24 (m, 2H), 1.88 (s, 3H) 1.80–1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 208.0, 162.1 (d, $J_{C\text{-}F}$=247.8 Hz), 136.3 (d, $J_{C\text{-}F}$=3.3 Hz), 128.1 (d, $J_{C\text{-}F}$=8.1 Hz), 116.1 (d, $J_{C\text{-}F}$=21.4 Hz), 59.3, 48.5, 40.1, 31.6, 25.0, 20.9; IR (Neat Film, NaCl): 2950, 1708, 1601, 1510, 1355, 1231, 1186, 1164 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{14}H_{16}FO_2$ [M+H]$^+$: 235.1134, found 235.1132; $[\alpha]_{\mathrm{D}}^{25}-0.3$ (*c* 1.5, $CHCl_3$, 90% ee).

8.6.4. (S)-3-Acetyl-3-(m-tolyl)cyclohexanone (64c)—Synthesized according to the general procedure, 0.22 mmol scale. Title compound isolated as an off-white solid (33 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 1H), 7.14–7.01 (m, 3H), 2.87 (dt, *J*=14.9, 1.6 Hz, 1H), 2.65 (dt, *J*=14.8, 1.2 Hz, 1H), 2.48–2.22 (m, 7H), 1.92–1.66 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 140.6, 138.9, 129.1, 128.3, 126.9, 123.3, 59.7, 48.6, 40.2, 31.4, 25.1, 21.5, 21.0; IR (Neat Film, NaCl): 2949, 1708, 1558, 1456, 1354, 1182, 1158 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1385, found 231.1383; $[\alpha]_D^{25} - 4.6$ (*c* 1.6, $CHCl_3$, 92% ee).

8.6.5. (S)-N-(5-(1-Acetyl-3-oxocyclohexyl)-2-methylphenyl)-2,2,2-trifluoroacetamide (64d)—Synthesized according to the general procedure, 0.22 mmol scale. Title compound isolated as an off-white solid (54 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.94 (m, 1H), 7.73 (dt, *J*=5.2, 2.5 Hz, 1H), 7.27 (t, *J*=4.0 Hz, 1H), 7.06 (dd, *J*=8.1, 2.0 Hz, 1H), 2.90 (d, *J*=14.9 Hz, 1H), 2.60 (d, *J*=15.0 Hz, 1H), 2.50–2.41 (m, 1H), 2.41–2.21 (m, 7H), 1.91 (s, 3H), 1.90–1.79 (m, 1H), 1.78–1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 208.0,155.1 (q, $J_{C\text{-}F}$=37.2 Hz),139.8, 133.7, 131.7,129.8, 125.1, 121.4, 115.9 (q, $J_{C\text{-}F}$=288.8 Hz), 59.6, 48.6, 40.0, 31.2, 25.1, 21.0, 16.9; IR (Neat Film, NaCl): 3279, 2954, 1708, 1541, 1506, 1356, 1256, 1201, 1158 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{17}H_{19}O_3F_3N$ $[M+H]^+$: 342.1317, found 342.1313; $[\alpha]_D^{25} 18.7$ (*c* 1.1, $CHCl_3$, 91% ee).

8.6.6. (S)-3-Acetyl-3-(m-tolyl)cyclopentanone (64f)—Synthesized according to the general procedure, the title compound was isolated as a pale yellow oil (31 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 1H), 7.14 (dddt, *J*=7.6, 1.9, 1.3, 0.6 Hz, 1H), 7.10–7.03 (m, 2H), 3.10 (ddd, *J*=18.0, 1.7, 0.8 Hz, 1H), 2.71 (dddd, *J*=13.0, 7.7, 5.5, 1.7 Hz, 1H), 2.57–2.49 (m, 1H), 2.46–2.27 (m, 6H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 207.9, 140.7, 138.9, 129.0, 128.50, 127.2, 123.5, 123.5, 47.1, 36.5, 30.8, 25.3, 21.5; IR (Neat Film, NaCl): 2921, 1745, 1704, 1605, 1489, 1407, 1354, 1150 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1229, found 217.1218; $[\alpha]_D^{25} 75.2$ (*c* 1.5, $CHCl_3$, 90% ee).

8.6.7. (S)-3-Acetyl-3-(4-fluorophenyl)cyclopentanone (64g)—Synthesized according to the general procedure, the title compound was isolated as a pale yellow oil (25 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.21 (m, 2H), 7.14–7.06 (m, 2H), 3.12 (dd, *J*=17.8, 1.7 Hz, 1H), 2.78–2.69 (m, 1H), 2.49 (dd, *J*=17.9, 0.9 Hz, 1H), 2.43–2.27 (m, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 207.4, 162.2 (d, $J_{C\text{-}F}$=247.8 Hz), 136.6 (d, $J_{C\text{-}F}$=3.3 Hz), 128.2 (d, $J_{C\text{-}F}$=8.2 Hz), 116.1 (d, $J_{C\text{-}F}$=21.5 Hz), 60.6, 47.2, 36.5, 30.9, 25.2; IR (Neat Film, NaCl): 2925, 1745, 1704, 1599, 1509, 1408, 1355, 1223, 1142 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{13}H_{14}O_2F$ $[M+H]^+$: 221.0978, found 221.0984; $[\alpha]_D^{25} 65.9$ (*c* 1.0, $CHCl_3$, 92% ee).

8.7. Representative procedure for the synthesis of *N*-trifluoroacetamide boronic acids

8.7.1. N-(3-Bromophenyl)-2,2,2-tri*fl*uoroacetamide—In a 100 mL round bottom flask were added consecutively 3-bromoaniline (1.7 g, 10.0 mmol, 1 equiv), DMAP (0.12 g, 1.0 mmol, 0.1 equiv), 20 mL of CH_2Cl_2 and Et_3N (1.7 mL, 12.0 mmol, 1.2 equiv). The solution was cooled to 0 °C and trifluoroacetic anhydride (2.1 mL, 15.0 mmol, 1.5 equiv) was added dropwise. The obtained mixture was stirred at room temperature until all the starting material was consumed (TLC hexane/EtOAc 4:1) and then it was extracted with CH_2Cl_2 (3 × 20 mL) and washed with brine (2 × 20 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated to give an off-white solid that was purified via silica gel column chromatography (2.35 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (t, J=2.0 Hz, 1H), 7.80 (br s, 1H), 7.51 (dd, J=8.1, 1.2 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.30–7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (q, $J_{C\text{-}F}$=37.7 Hz), 136.3, 130.7, 129.7, 123.8, 123.0, 119.3, 115.6 (q, $J_{C\text{-}F}$=288.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.72, −75.73; FTIR (Neat Film, NaCl) 3288, 1709, 1593, 1538, 1470, 1429, 1338, 1263, 1251, 1171, 1153, 1069, 997, 975, 925, 873, 865, 785, 739 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_8H_5BrF_3NO$ $[M-H]^-$: 265.9434, found: 295.9426.

8.7.2. 3-(2,2,2-Trifluroacetamide)-phenylboronic acid (65f)—A flame dried one neck round bottom flask was charged with the required trifluoroacetanilide (1.0 g, 3.7 mmol, 1 equiv). The flask was sealed, evacuated, and backfilled with argon. THF (20 mL) was added via syringe and the obtained mixture was cooled to −78 °C. *n*-BuLi (2.3 M solution in hexane, 3.6 Ml, 8.2 mmol, 2.2 equiv) was added dropwise and the obtained mixture was stirred for 2 h at this temperature. Triisopropylborate (2.7 mL, 11.7 mmol, 3 equiv) was then added via syringe and the mixture was stirred for 10 min at −78 °C and for 1 h at room temperature. A solution of HCl (2 M in water, 10 mL) was added and the biphasic mixture was vigorously stirred for another hour and then extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (2 × 20 mL) and dried over $MgSO_4$. Upon evaporation of the solvent under reduced pressure an off-white solid was obtained. It was suspended in hexane and stirred until a fine powderwas formed. Itwas filtered and dried in high vacuum for 30 min (0.58 g, 67% yield). (General note for all trifluoroacetamide substrates: If the obtained product is not clean from NMR analysis then a 10:1 mixture of hexane/Et_2O or hexane/CH_2Cl_2 can be used instead of hexanes to suspend the compound. If the crude aryl boronic acid is obtained as an oil and does not solidify, then add ether, water, and a 1Msolution of NaOH (5 equiv) to the crude mixture. After extraction, the isolated water phase can be acidified with a 1 M aqueous HCl solution and extracted with EtOAc. The organic phased is washed with water, brine, and concentrated in vacuo. Upon evaporation of the solvent and trituration with pentane or hexane the desired product should be obtained as an off-white solid.) ^{1}H NMR (300 MHz, acetone-d_6) δ 8.11 (br s, 1H), 7.81 (m, 1H), 7.74 (dt, J=7.4, 1.0 Hz, 1H), 7.40 (t, J=7.7 Hz, 1H), 7.28 (s, 1H); (The obtained ^{13}C NMR is complex due to the presence of two rotamers in solution) ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (q, J=36.9 Hz), 154.7 (q, J=36.8 Hz), 135.8, 135.7, 131.5, 128.2, 126.7, 126.6, 123.0, 122.9, 116.2 (q, J=288.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.22, −76.25; FTIR (Neat Film, NaCl): 3305, 1701, 1585, 1554, 1437, 1334, 1264, 1182, 1031, 780 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_8H_7BrF_3NO$ $[M-H]^-$: 231.0435, found: 231.0433.

8.7.3. 4-(2,2,2-Trifluroacetamide)-phenylboronic acid (65c)—Obtained using the representative procedure in 65% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.22 (br s, 1H), 7.91 (d, *J*=8.4 Hz, 2H), 7.72 (d, *J*=8.4 Hz, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 155.6 (q, $J_{C\text{-}F}$=37.2 Hz), 136.3, 139.2, 135.9, 120.5, 119.2 (q, J_{CF} =288.3 Hz); ^{19}F NMR (282 MHz, acetone-d_6) δ −76.21, −76.24; FTIR (Neat Film, NaCl) 3297, 1714, 1595, 1539, 1408, 1275, 1244, 1183, 1113, 1008, 832, 798 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_8H_7BrF_3NO$ [M−H]$^-$: 231.0435, found: 231.0443.

8.7.4. 4-(2,2,2-Trifluroacetamide)-3-methoxyphenylboronic acid (65d)—Obtained as an off-white solid in 35% yield following the general procedure and using the required trifluoroacetanilide (1.4 g, 4.9 mmol, 1 equiv), *n*-BuLi (4.4 mL of a 2.4 M solution, 10.7 mmol, 2.2 equiv) and triisopropylborate (3.4 mL, 14.6 mmol, 3 equiv). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.34 (s, 1H), 8.05 (dd, *J*=3.0, 6.9 Hz, 1H), 7.58 (s 1H), 7.54 (dd, *J*=7.9,1.0 Hz, 1H) 7.29 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.3 (q, $J_{C\text{-}F}$ =150 Hz), 149.3, 126.8, 126.6, 120.5, 116.1, 115.8 (q, $J_{C\text{-}F}$=288 Hz), 112.5, 55.4; IR (Neat Film, NaCl): 3298, 1708, 1591, 1537, 1503, 1465, 1404, 1342, 1294, 1273, 1224, 1161, 1123, 1015; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_9H_8BO_4NF_3$ [M−H]$^-$: 261.0590, found: 261.0497.

8.7.5. 4-(2,2,2-Trifluroacetamide)-2,6-dimethyl-phenylboronic acid (65e)— Obtained as an off-white solid in 66% yield following the general procedure and using the required trifluoroacetanilide (1.0 g, 3.4 mmol, 1 equiv), *n*-BuLi (3.2 mL of a 2.3 M solution, 7.44 mmol, 2.2 equiv) and triisopropylborate (2.3 mL, 10.1 mmol, 3 equiv). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.62 (s, 2H), 7.20 (s, 1H), 2.25 (s, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 155.1 (q, *J*=36.5 Hz), 134.2, 134.2, 134.1, 133.9, 116.5 (q, *J*=286.0 Hz), 17.1; ^{19}F NMR (282 MHz, acetone-d_6) δ −75.97, −75.99; FTIR (Neat Film, NaCl): 3233, 1705, 1602, 1533, 1340, 1219, 1192, 1160 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{10}H_{11}NBrF_3O$ [M−H]$^-$: 259.0748, found 259.0749.

8.7.6. 3-(2,2,2-Trifluroacetamide)-4-methylphenylboronic acid (65g)—Obtained as an off-white solid in 66% yield following the general procedure and using the required trifluoroacetanilide (2.0 g, 3.7 mmol, 1 equiv), *n*-BuLi (3.6 mL of a 2.3 M solution, 8.2 mmol, 2.2 equiv) and triisopropylborate (2.6 mL, 11.2 mmol, 3 equiv). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.82 (s, 1H), 7.75 (dd, *J*=6.5, 10 Hz, 1H), 7.32 (d, *J*=7.5 Hz, 1H) 7.24 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 155.4 (q, *J*=37.5 Hz), 136.2, 133.5, 132.9, 132.1,130.1,116.4 (q, *J*=288.0 Hz); FTIR (Neat Film, NaCl) 3270,1708, 1617, 1533, 1406, 1351, 1259, 1180, 1162, 1092, 1036, 898, 825 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_9H_8BF_3NO_3$ [M−H]$^-$: 245.0477, found 245.0591.

8.8. Representative general procedure for the enantioselective 1,4-addition of arylboronic acids to β-substituted cyclic enones

8.8.1. (R)-3-(4-(2,2,2-Tri fluoroacetamide)phenyl)-3-methylcyclohexanone (66c) —A screw-top 5 mL vial was charged with a stir bar, Pd(OCOF$_3$)$_2$ (4.5 mg, 0.014 mmol, 0.05 equiv), (*S*)-*t*-BuPyOx (3.3 mg, 0.016 mmol, 0.06 equiv), boronic acid (95 mg, 0.41 mmol, 1.5 equiv), and NH_4PF_6 (13 mg, 0.08 mmol, 0.3 equiv). Dichloroethane (1 mL) was added and the mixture was stirred until a homogeneous suspension was formed (1 min). 3-Methyl-2-cyclohexenone (30 mg, 0.27 mmol, 1 equiv) was then added dissolved in 1.7 mL of dichloroethane (yields are improved with the addition of enone as a solution). Water (25 μL, 1.3 mmol, 5 equiv) was added, and the vial was sealed and the reaction was stirred at 60 °C for 3 h. After this time almost all the solid in the vial was consumed and from TLC (hexane/EtOAc 4:1) all the starting enone disappeared. The mixture was cooled to ambient temperature and it was charged directly into a silica gel column for purification. The desired product was isolated as white powder (80 mg, 98% yield, 89% ee SFC column 6 (IC) 5 mL/min 4% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.53 (m, 2H), 7.36 (m, 2H), 2.85 (d, *J*=14.2 Hz, 1H), 2.45 (d, *J*=14.0 Hz, 1H), 2.32 (m, 2H), 2.25–2.12 (m, 1H), 1.98–1.82 (m, 2H), 1.71–1.57 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 154.9 (q, *J*=37.4 Hz), 145.2, 133.5, 126.7, 120.6, 115.7 (q, *J*=289.0 Hz), 52.9, 42.9, 40.7, 37.9, 30.4, 22.0; FTIR (Neat Film, NaCl) 3292, 2958, 1706, 1609, 1545, 1517, 1412, 1285, 1252, 1193, 1155, 901, 835 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{16}F_3NO$ $[M-H]^-$: 298.106, found 289.1049; $[\alpha]_D^{25} - 47.5$ (*c* 2.10, $CHCl_3$, 89% ee).

8.8.2. (R)-3-(4-(N-Carbobenzyloxy)phenyl)-3-methylcyclohexanone (66a)— Following the general procedure the desired product was obtained as a clear oil (35 mg, 45% yield, 76% ee, SFC column 6 (IC) 5 mL/min 15% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (m, 6H), 7.25–7.22 (m, 3H), 6.63 (br s,1H), 5.20 (s, 2H), 2.84 (d, *J*=14.2 Hz, 1H), 2.42 (d, *J*=14.1 Hz, 1H), 2.31 (m, 2H), 2.21–2.10 (m, 1H), 1.95–1.80 (m, 2H),1.73–1.60 (m, 1H),1.30 (s, 3H); ^{13}CNMR(125 MHz, $CDCl_3$) δ 211.6, 153.5, 142.7, 136.1, 135.9, 128.7, 128.5, 128.4, 126.5, 118.9, 67.2, 53.3, 42.6, 40.9, 38.0, 30.1, 22.1; FTIR (Neat Film, NaCl) 3306, 2953, 1705, 1597, 1534, 1454, 1409, 1323, 1220, 1052 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1756, found 338.1760; $[\alpha]_D^{25} - 26.8$ (*c* 1.40, $CHCl_3$, 76% ee).

8.8.3. (R)-3-(4-(N-Pivaloyl)phenyl)-3-methylcyclohexanone (66b)— Following the general procedure the desired product was obtained as a white solid (56 mg, 72% yield, 78% ee SFC column 5 (OB–H) 5 mL/min 10% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J*=8.7 Hz, 2H), 7.33–7.24 (m, 2H), 2.85 (d, *J*=14.2 Hz, 1H), 2.42 (d, *J*=14.2 Hz, 1H), 2.31 (m, 2H), 2.21–2.11 (m, 1H), 1.95–1.80 (m, 2H), 1.72–1.58 (m, 1H), 1.31 (s, 9H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 176.7, 143.4, 136.2, 126.3, 120.1, 53.2, 42.7, 40.9, 39.7, 38.1, 30.1, 27.8, 22.1; FTIR (Neat Film, NaCl) 3379, 2961, 1685, 1594, 1518, 1400, 1318, 1301, 1255, 1189 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{18}H_{26}NO_2$ $[M+H]^+$: 288.1964, found 288.1969; $[\alpha]_D^{25} - 52.5$ (*c* 1.01, $CHCl_3$, 78% ee).

8.8.4. (R)-3-(4-(2,2,2-Trifluoroacetamide)-3-methoxyphenyl)-3-methylcyclohexanone (66d)— Following the general procedure the desired product was obtained as white solid (67 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 8.24 (d, *J*=8.5 Hz, 2H), 6.96 (dd, *J*=8.5, 2.1 Hz, 1H), 6.87 (d, *J*=2.1 Hz, 1H), 3.93 (s, 3H), 2.87 (d, *J*=14.1 Hz, 1H), 2.45 (d, *J*=14.2 Hz, 1H), 2.32 (m, 1H), 2.24–2.14 (m, 1H), 2.0–1.8 (m, 1H), 1.68–2.5 (m, 1H), 1.32 (s, 3H); FTIR (neat, NaCl): 3362, 2960, 2871, 1706, 1665, 1594, 1515, 1479, 1402, 1321, 1228, 1193, 1164 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{16}H_{17}F_3NO_3$ [M−OH]: 328.1161, found: 328.1167; $[\alpha]_D^{25} - 61.3$ (*c* 1.25, $CHCl_3$, 88% ee).

8.8.5. (R)-3-(4-(2,2,2-Trifluoroacetamide)-2,6-dimethylphenyl)-3-methylcyclohexanone (66e)—Following the general procedure the desired product was obtained in 93% yield as a white solid (90% ee, SFC column 1 (AD-H) 5 mL/min 5% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.05 (s, 2H), 2.84 (d, *J*=14.2 Hz, 1H), 2.42 (d, *J*=14.1 Hz, 1H), 2.32 (m, 2H), 2.24 (s, 6H), 2.21–2.10 (m, 1H), 1.96–1.80 (m, 2H), 1.76–1.60 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 156.2 (q, *J*=36.4 Hz), 147.6, 135.1, 128.9, 125.7, 118.2 (q, *J*=279.9 Hz), 52.8, 42.4, 40.6, 37.6, 29.4, 21.9, 18.2; FTIR (Neat Film, NaCl) 2958, 2863, 1715, 1651, 1583, 1568, 1538, 1479, 1441, 1359, 1314, 1228, 1198, 1157, 1101 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{17}H_{20}F_3NO_2$ [M−H]$^-$: 326.1373, found 326.1370; $[\alpha]_D^{25} - 54.3$ (*c* 2.10, $CHCl_3$, 90% ee).

8.8.6. (R)-3-(3-(2,2,2-Tri fluoroacetamide)phenyl) - 3 - methylcyclohexanone (66f)—Following the general procedure the desired product was obtained in 60% yield as transparent oil (92% ee, SFC column 1 (AD-H) 5 mL/min 5% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.55–7.45 (m, 2H), 7.36 (t, *J*=7.9 Hz, 1H), 7.20 (m, 1H), 2.87 (d, *J*=14.2 Hz, 1H), 2.46 (d, *J*=14.2 Hz, 1H), 2.32 (m, 2H), 2.27–2.17 (m, 1H),1.98–1.82 (m, 2H),1.71–1.57 (m, 1H),1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 154.9 (q, *J*=37.0 Hz), 148.9, 135.5, 129.5, 123.6, 118.5, 118.0, 115.6 (q, *J*=289.2 Hz), 52.9, 43.0, 40.7, 37.8, 30.0, 22.0; FTIR (Neat Film, NaCl) 3298, 3157, 3111, 2959, 2876,1713, 1616, 1595, 1563, 1493, 1442, 1421, 1291, 1239, 1201, 1156 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{15}H_{16}F_3NO_2$ [M−H]$^-$: 298.1055, found: 298.1050; $[\alpha]_D^{25} - 28.9$ (*c* 2.10, $CHCl_3$, 92% ee).

8.8.7. (R)-3-(3-(2,2,2-Trifluoroacetamide)-4-methylpheny)-3-methylcyclohexanone (66g)—Following the general procedure the desired product was obtained in 77% yield as a white solid (91% ee, OD-H column, 5 mL/min, 5% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.66 (s, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 7.11 (dd, *J*=8.1, 1.9 Hz, 1H), 2.85 (d, *J*=14.1 Hz, 1H), 2.44 (d, *J*=14.1 Hz, 1H), 2.32 (m, 2H), 2.26 (s, 3H), 2.24–2.07 (m, 1H), 1.97–1.80 (m, 2H), 1.78–1.60 (m, 1H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 156.2 (q, *J*=36.4 Hz), 146.6, 132.9, 131.4, 130.9, 128.3, 124.4, 118.1 (q, *J*=279.8 Hz), 53.0, 42.7, 40.7, 37.7, 29.6, 22.0, 16.9; FTIR (Neat Film, NaCl) 3277, 3060, 2959, 2873, 1711, 1617, 1577, 1540, 1507, 1452, 1420, 1316, 1281, 1257, 1200, 1162 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calcd for $C_{16}H_{18}F_3NO_2$ [M+H]$^+$: 314.1362, found: 314.1370. $[\alpha]_D^{25} - 45.6$ (*c* 5.3, $CHCl_3$, 88% ee).

Supplementary Material

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Acknowledgments

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9. (a) Shintani R, Tsutsumi Y, Nagaosa M, Nishimura T, Hayashi T. J Am Chem Soc. 2009; 131:13588. [PubMed: 19728707] (b) Shintani R, Takeda M, Nishimura T, Hayashi T. Angew Chem Int Ed. 2010; 49:3969.
10. The same group also reported additions to β,β-disubstituted α,β-unsaturated esters, see: Shintani R, Hayashi T. Org Lett. 2011; 13:350. [PubMed: 21128681]
11. A recent paper describing the use of a Rh·OlefOx (olefin-oxazoline) complex provided a single example of a phenylboronic acid addition to 3-methylcyclohexen-2-one (i.e., 1+2→3). Unfortunately, ketone **3** was isolated in only 36% yield and 85% ee, see: Hahn BT, Tewes F, Fröhlich R, Glorius F. Angew Chem Int Ed. 2010; 49:1143.

12. For excellent review articles, see: Gutnov A. Eur J Org Chem. 2008:4547.; Christoffers J, Koripelly G, Rosiak A, Rössle M. Synthesis. 2007:1279.; For a recent example, see: Xu Q, Zhang R, Zhang T, Shi M. J Org Chem. 2010; 75:3935. [PubMed: 20446712]
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16. The absolute stereochemistry for all products shown was assigned by analogy to the product from Table 2, entry 2 as described in Ref. 3c.
17. See Experimental section.
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21. (a) 3-Ethylcyclohex-2-enone.[5b] (b) 3-Isopropylcyclohex-2-enone, 3-methylcyclohept-2-enone: Martin NJA, List B. J Am Chem Soc. 2006; 128:13368. [PubMed: 17031944] ; (c) 3-Butylcyclohex-2-enone: Moritani Y, Appella DH, Jurkauskas V, Buchwald SL. J Am Chem Soc. 2000; 122:6797.; (d) 3-Cyclopropylcyclohex-2-enone: Piers E, Banville J, Lau CK, Nagakura I. Can J Chem. 1982; 60:2965.; (e) 3-Benzylcyclohex-2-enone: Wang X, Reisinger CM, List B. J Am Chem Soc. 2008; 130:6070. [PubMed: 18422314] ; (f) [1,1′-Bi(cyclohexan)]-1-en-3-one: Yeh MC, Knochel P, Butler WM, Berk SC. Tetrahedron Lett. 1988; 29:6693.; (g) 3-(3-(Benzyloxy) propyl)cyclohex-2-enone: Kim S, Koh JS. J Chem Soc Chem Commun. 1992:1377.; (h) 3-Acetylcyclohex-2-enone, 3-acetylcyclopent-2-enone: Catino AJ, Forslund RE, Doyle MP. J Am Chem Soc. 2004; 126:13622. [PubMed: 15493912]
22. (a) *i*-PrPyOx: Frauenlob R, McCormack MM, Walsh CM, Bergin E. Org Biomol Chem. 2011; 9:6934. [PubMed: 21904763] ; (b) PhPyOx: Malkov AV, Stewart-Liddon AJP, McGeoch GD, Ramirez-Lopez P, Kocovsk P. Org Biomol Chem. 2012; 10:4864. [PubMed: 22595994] ; (c) *i*-BuPyOx, 5-PhPyOx[14] (d) 4-OMePyOx, 4-CF_3PyOx: Jensen KH, Webb JD, Sigman MS. J Am Chem Soc. 2010; 132:17471. [PubMed: 21082845] ; (e) *t*-BuQuinOx: He W, Yip K-T, Zhu N-Y, Yang D. Org Lett. 2009; 11:5626. [PubMed: 19905004] ; (f) *i*-PrQuinOx: Zhang Y, Sigman MS. J Am Chem Soc. 2007; 129:3076. [PubMed: 17298071]
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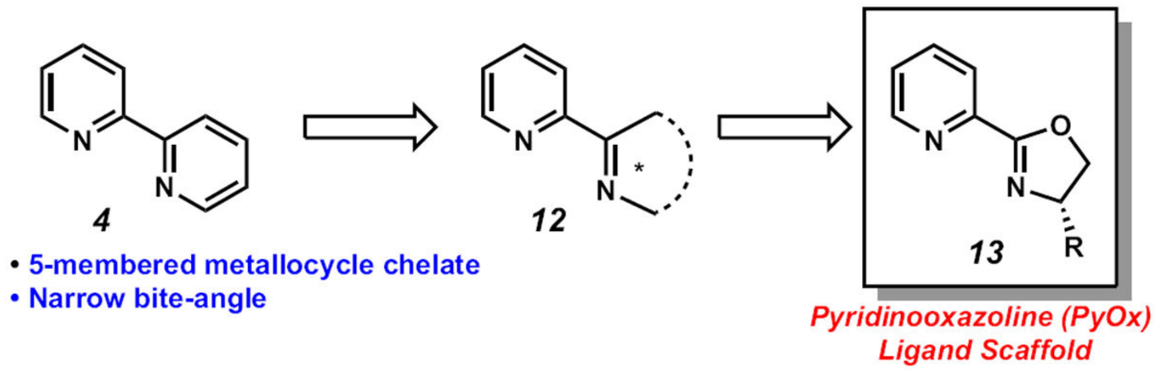


Fig. 1.
Logical implementation of pyridinooxazoline ligands.

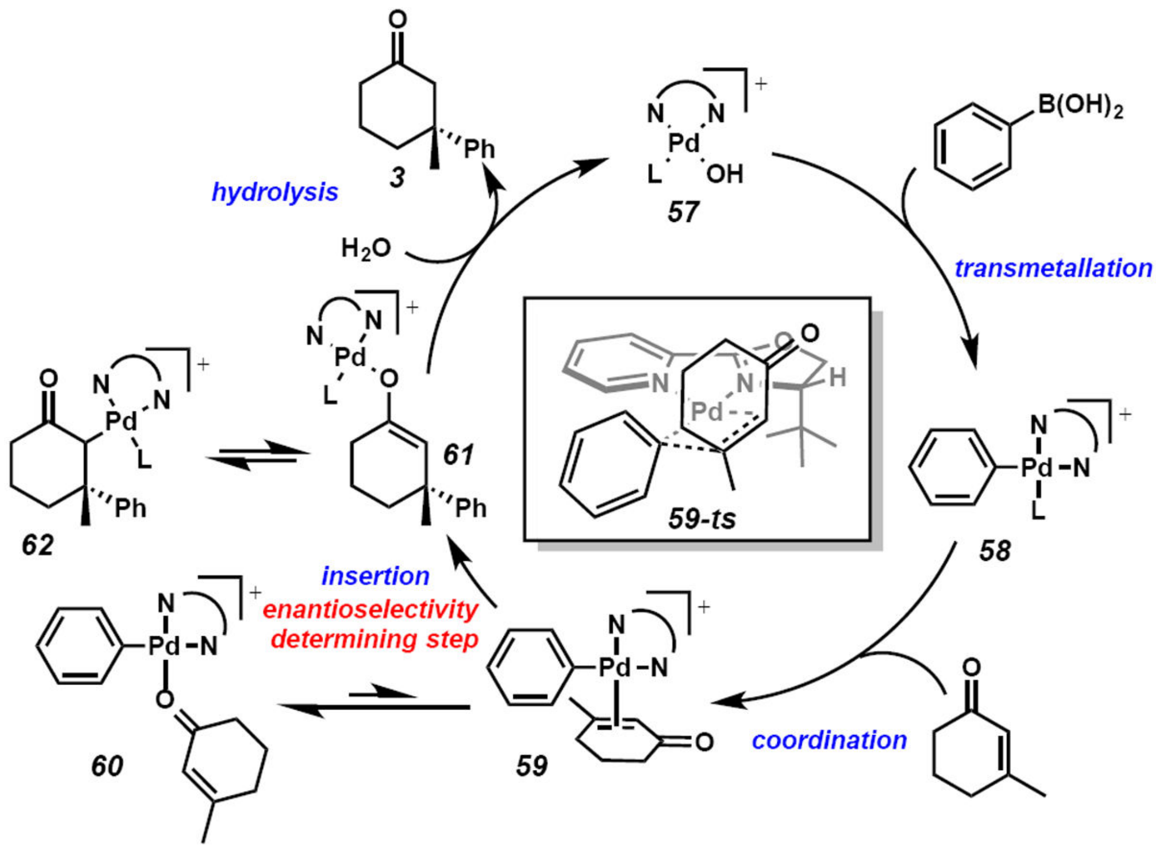
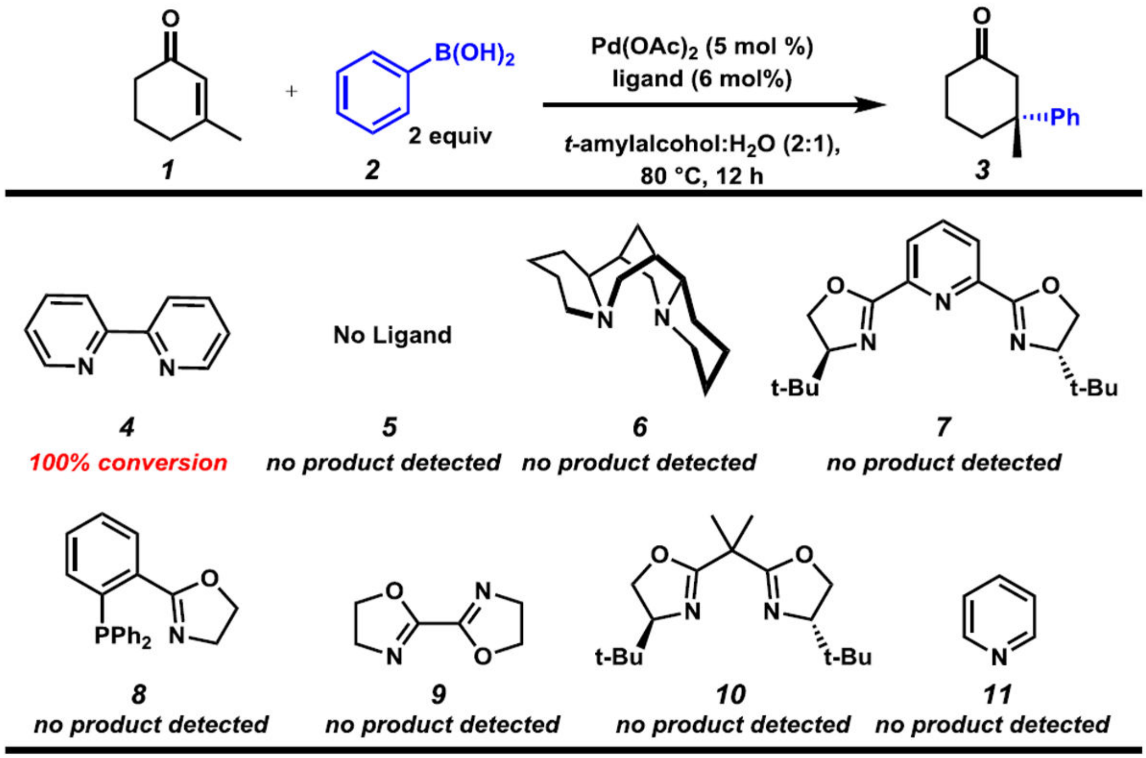


Fig. 2.
Plausible catalytic cycle.

Table 1

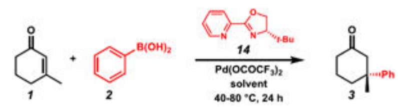
Preliminary ligand screen[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OAc)_2$ (5 mol%), and ligand (6 mol%) in solvent (1 mL) for 24 h. NMR yield. ee determined by chiral HPLC.

Table 2

Preliminary solvent screen[a]



Entry	Solvent	Temp (°C)	Yield (%)	ee[d] (%)
1	*tert*-Amyl alcohol	40	14[b]	–
2	Dioxane	40	17[b]	–
3	THF	40	31[b]	–
4	Toluene	40	65[b]	82
5	CH_2Cl_2	40	87[c]	91
6	Toluene	60	63[c]	77
7	Hexane	60	68[c]	62

[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol %), and (*S*)-*t*-BuPyOx (6 mol %) in solvent (1 mL) for 24 h.

[b]NMR yield.

[c]Isolated yield.

[d]ee determined by chiral HPLC.

Table 3

Optimization of palladium source[a]

Entry	Pd source	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	$PdCI_2$	CH_2CI_2	40	–	–
2	$Pd(MeCN)_2CI_2$	CH_2CI_2	40	–	–
3[d]	$Pd(MeCN)_2CI_2$, AgOTf	CH_2CI_2	40	69	17
4	$Pd(OAc)_2$	CH_2CI_2	40	65	92
5	$Pd(OCOCF)_2$	CH_2CI_2	40	87	91
6	$Pd(OCOCF_3)_2$	$CICH_2CH_2CI$	60	99	93
7[e]	$Pd(OCOCF_3)_2$	$CICH_2CH_2CI$	60	99	91
8[f]	$Pd(OCOCF)_2$	$CICH_2CH_2CI$	60	99	93

[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol %), and ligand **14** (6 mol %) in solvent (1 mL) for 12 h, unless otherwise noted.

[b]Isolated yield.

[c]ee determined by chiral HPLC.

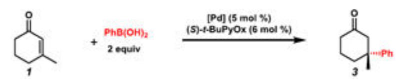
[d]12 mol % AgOTf.

[e]Reaction performed in the presence of added H_2O (2.5 mmol, 10 equiv).

[f]Phenylboronic acid loading reduced to 1.1 equiv.

Table 4

Polar solvents screen[a]



Entry	Solvent	Metal source	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	DCE	$Pd(OAc)_2$	60	Low	–
2	Acetone	$Pd(TFA)_2$	60	–	–
3	DMF	$Pd(TFA)_2$	60	–	–
4	MeOH	$Pd(CH,CN)_4(BF4)_2$	60	Trace	–
5	MeOH	$Pd(CH_3CN)_4(BF4)_2$	25	–	–
6	DCE-MeOH	$Pd(CH_3CN)_4(BF4)_2$	25	–	–
7	Acetone	*t*-BuPyOXPdCI2—NaPF6	25	–	–

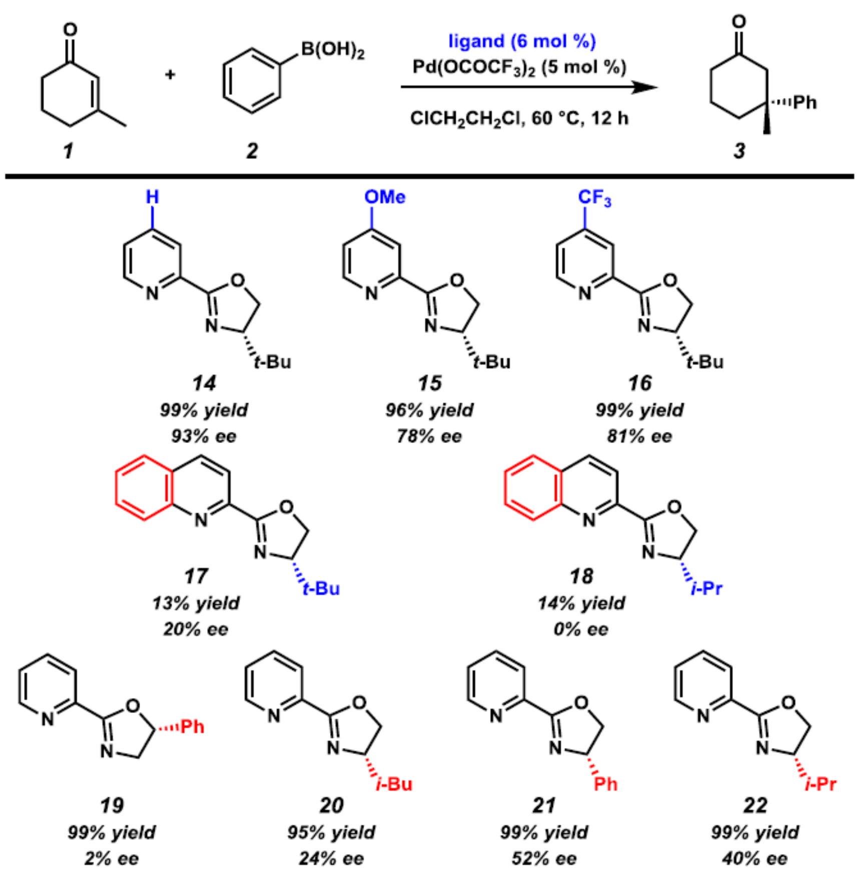
[a] Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), Pd(OCOCF3)2 (5 mol %), and ligand **14** (6 mol %) in solvent (1 mL) for 12 h.

[b] Isolated yield.

[c] ee determined by chiral HPLC.

Table 5

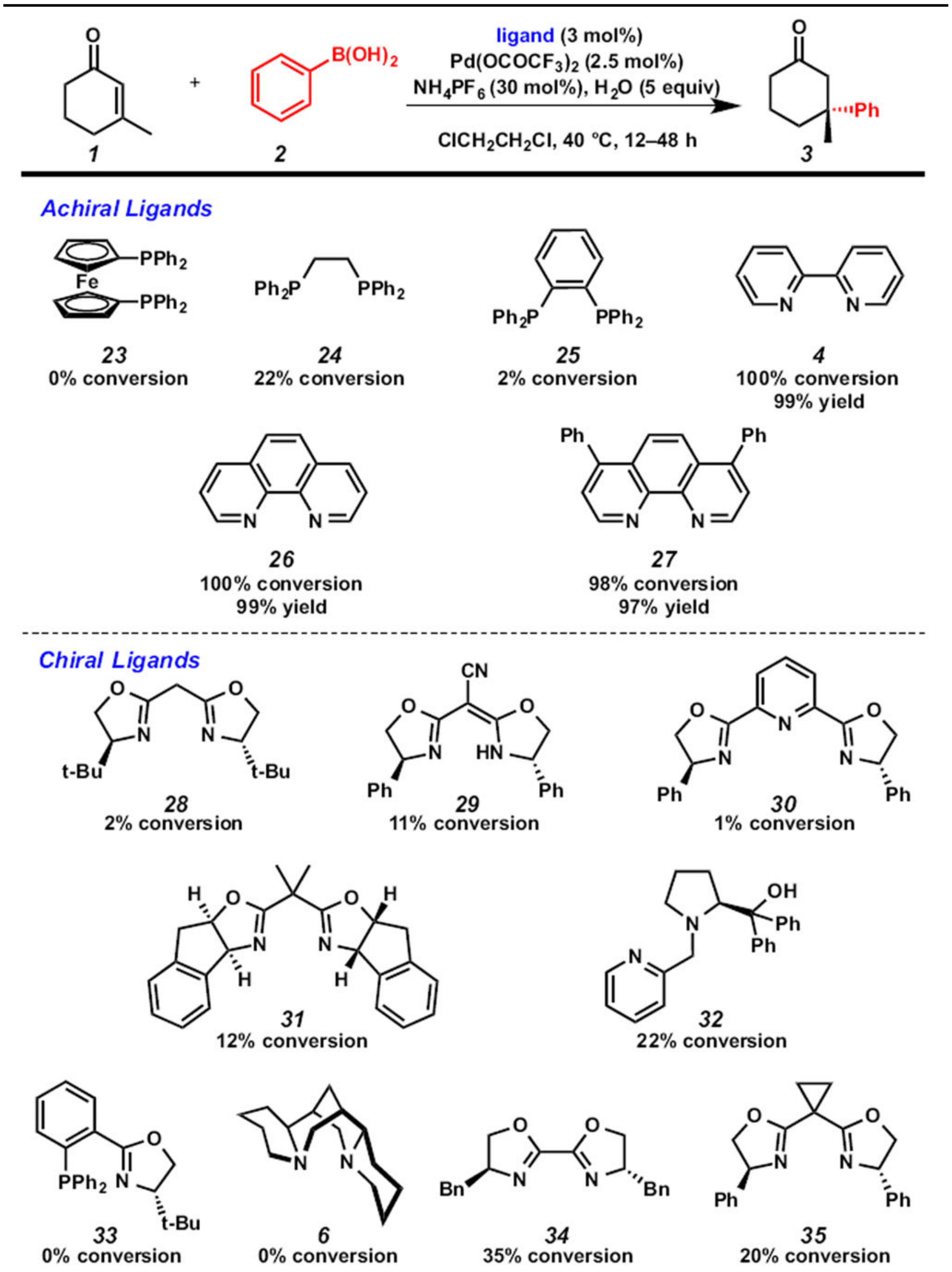
PyOx and QuinOx ligand screen[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol%), and ligand (6 mol%) in $ClCH_2CH_2Cl$ (1 mL) for 12 h. Isolated yield. ee determined by chiral HPLC.

Table 6

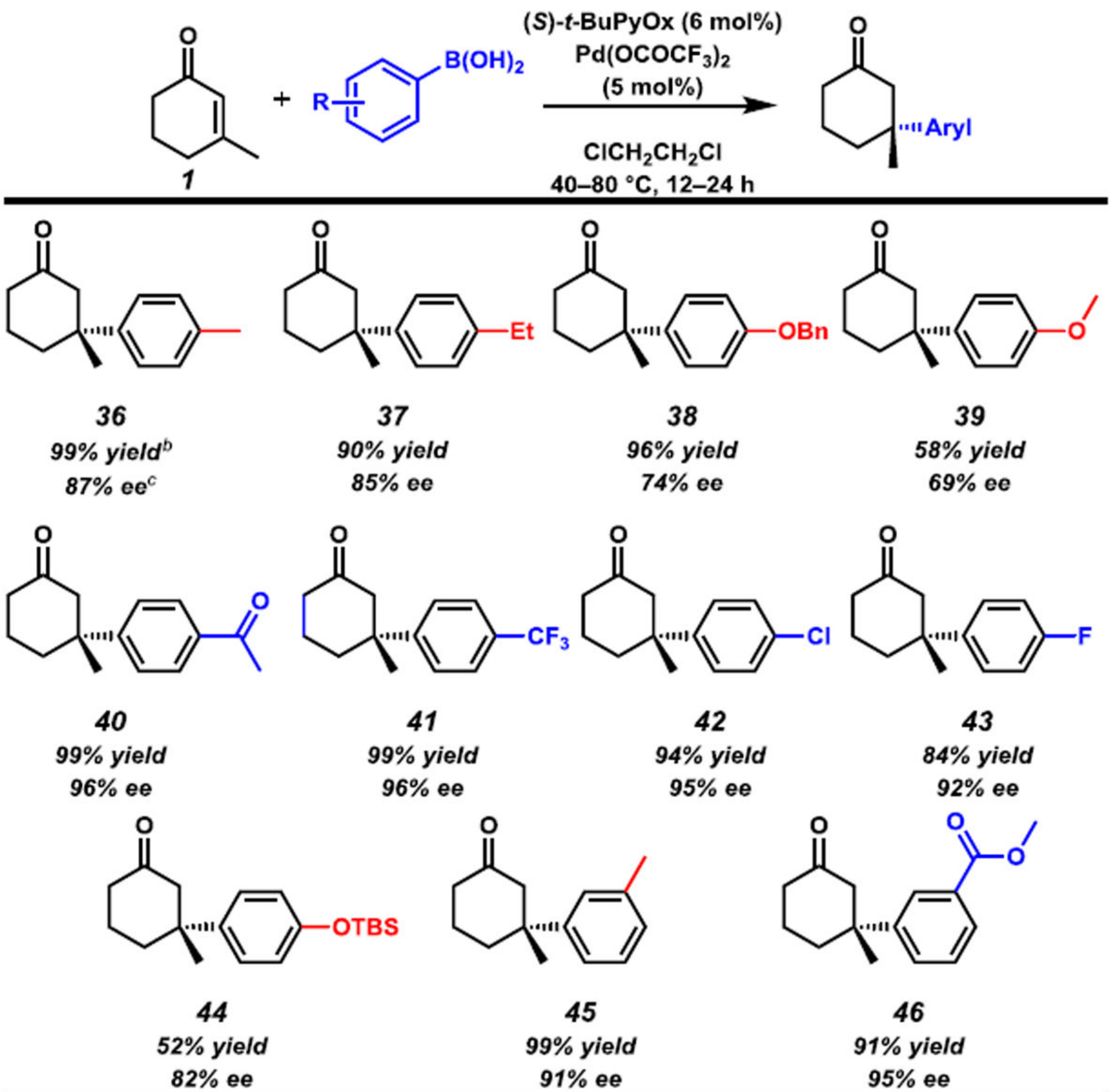
Expanded ligand screen[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OCOCF_3)_2$ (2.5 mol %), and ligand (3 mol%) in $ClCH_2CH_2Cl$ (1 mL) for 12–48 h, unless otherwise noted. Conversion determined by ^1H NMR.

Table 7

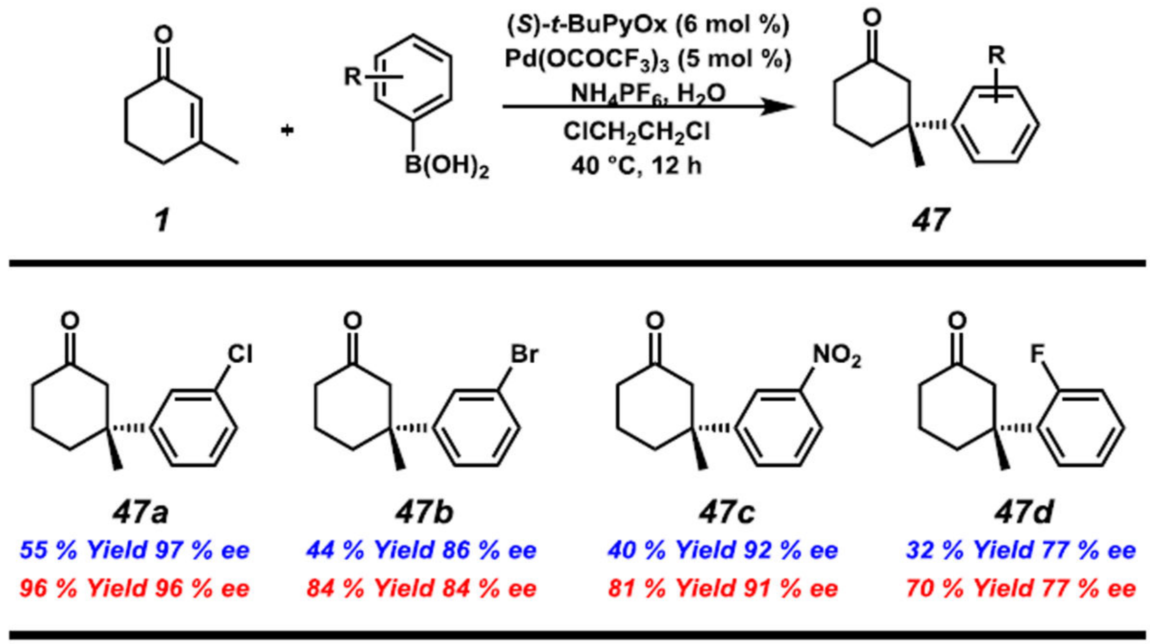
Boronic acid substrate scope[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexen-2-one (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol%), and ligand **14** (6 mol%) in $ClCH_2CH_2Cl$ (1 mL) at 40–80 °C for 12–24 h. Isolated yield. ee determined by chiral HPLC.

Table 8

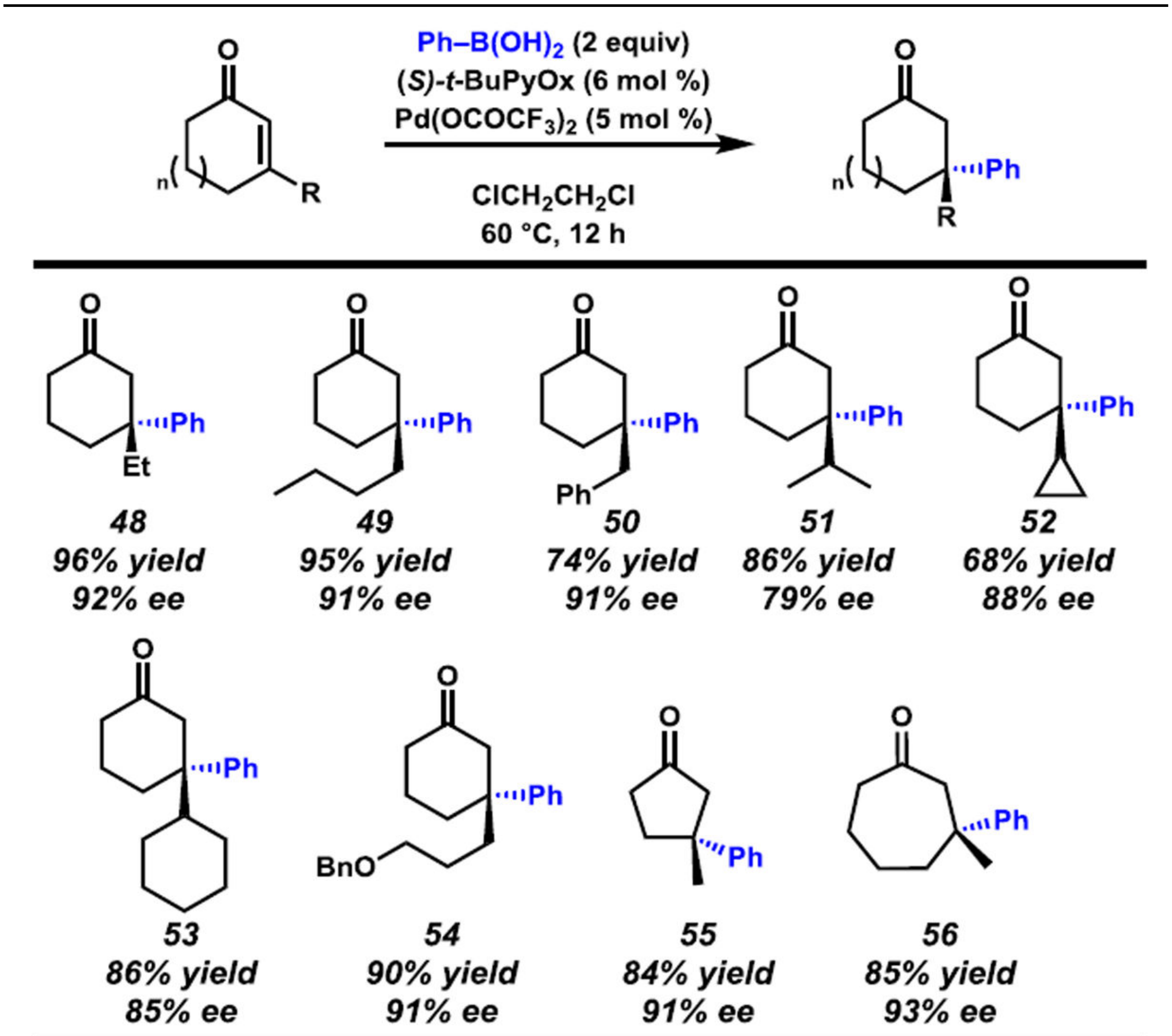
Increased reaction yields with NH_4PF_6 and water as reaction additives[a]



[a]Blue font: reported yield and ee of **47** in the absence of NH_4PF_6 and water with reactions performed at 60 °C; red font: yield and ee of **47** with additives. Conditions: Reactions were performed with phenylboronic acid (1.0 mmol), 3-methylcyclohexen-2-one (0.5 mmol), NH_4PF_6 (30 mol %), water (5 equiv.), $Pd(OCOCF_3)_2$ (5 mol%), and (*S*)-*t*-BuPyOx (6 mol%) in $ClCH_2CH_2Cl$ (2 mL) at 40 °C. Isolated yield. ee was determined by chiral HPLC.

Table 9

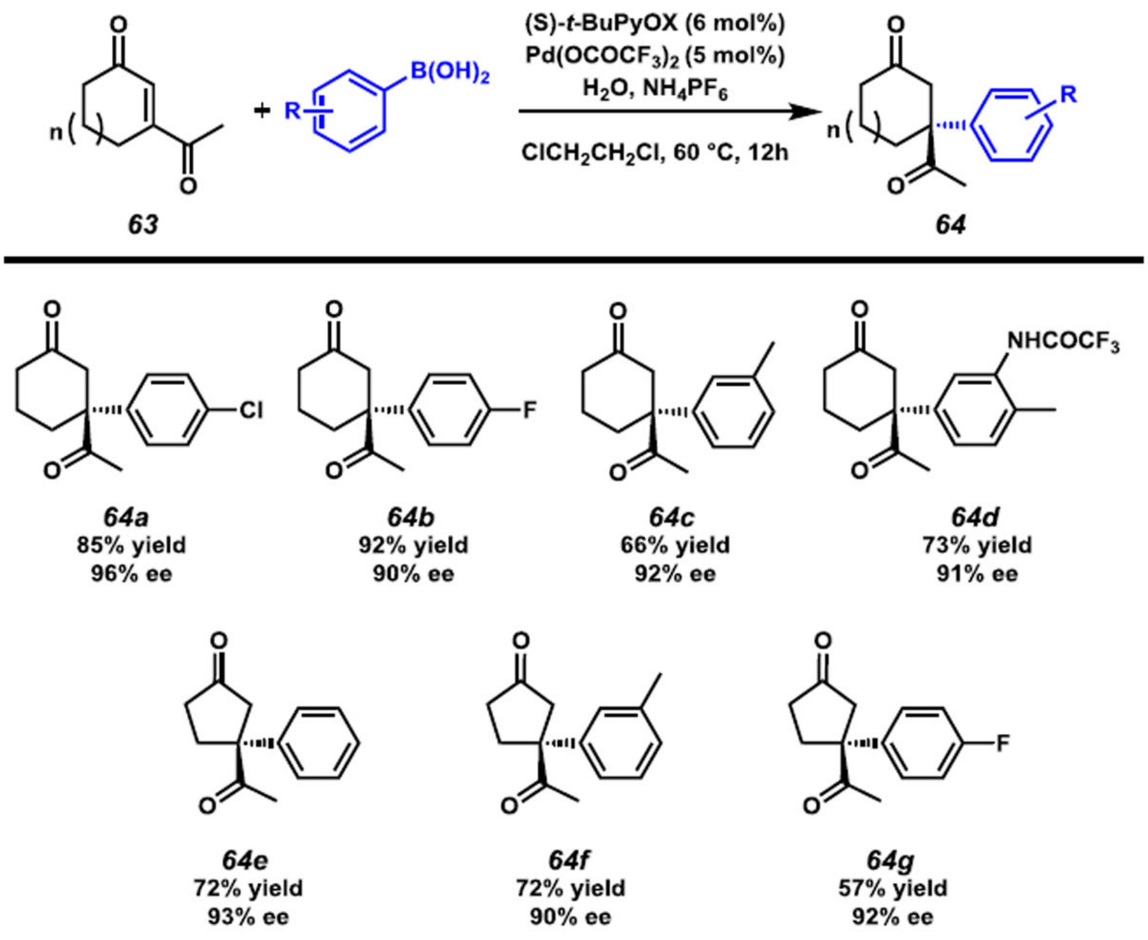
Enone substrate scope[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), cycloalkenone (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol%), and ligand **14** (6 mol%) in $ClCH_2CH_2Cl$ (1 mL) at 60 °C for 12 h.

Table 10

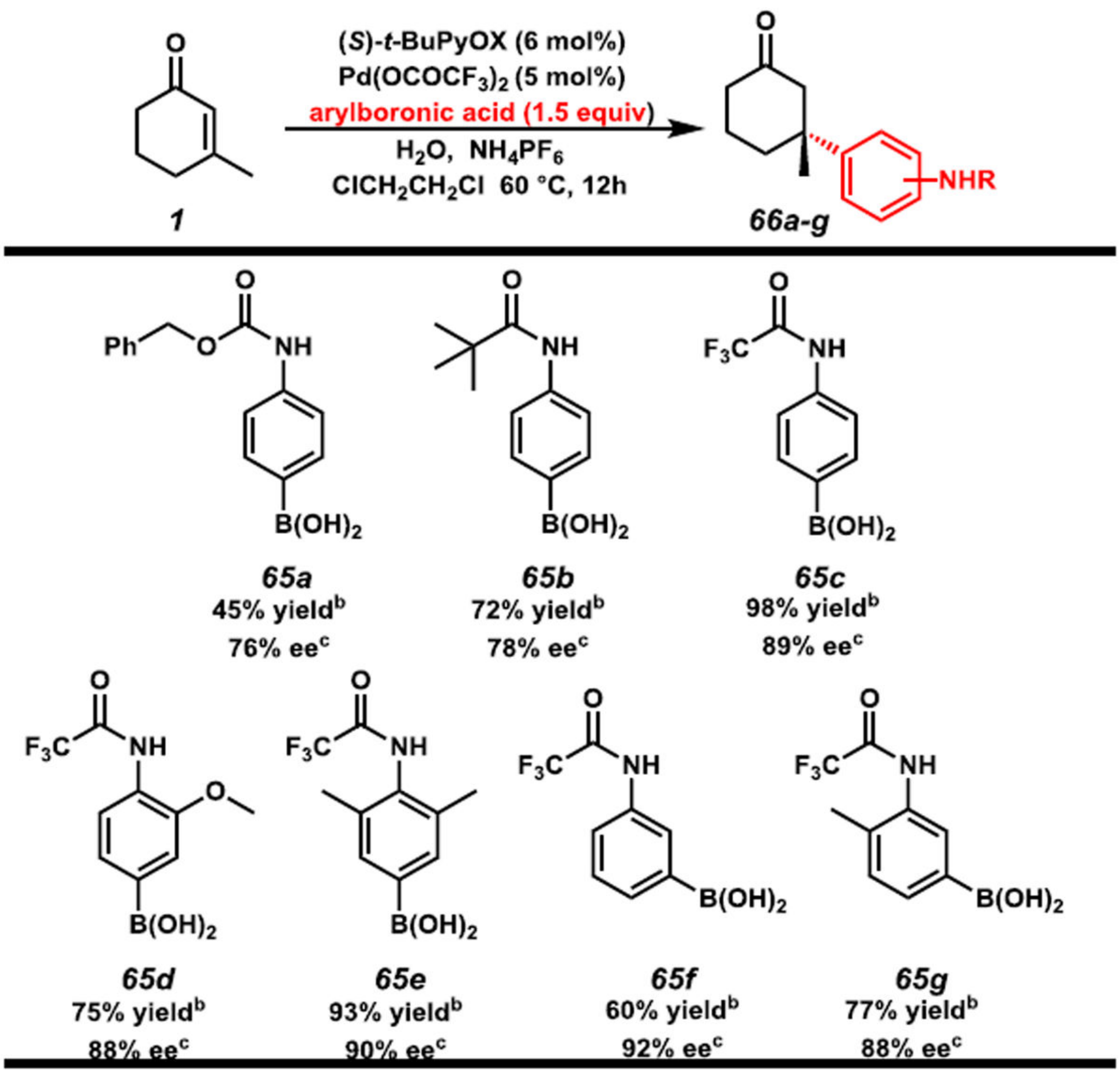
β-Acyl enone substrate scope[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), cycloalkenone (0.25 mmol), $Pd(OCOCF_3)_2$ (5 mol%), and ligand **14** (6 mol%) in $ClCH_2CH_2Cl$ (1 mL) at 60 °C for 12 h.

Table 11

Trifluoroacetamide boronic acid nucleophiles[a]



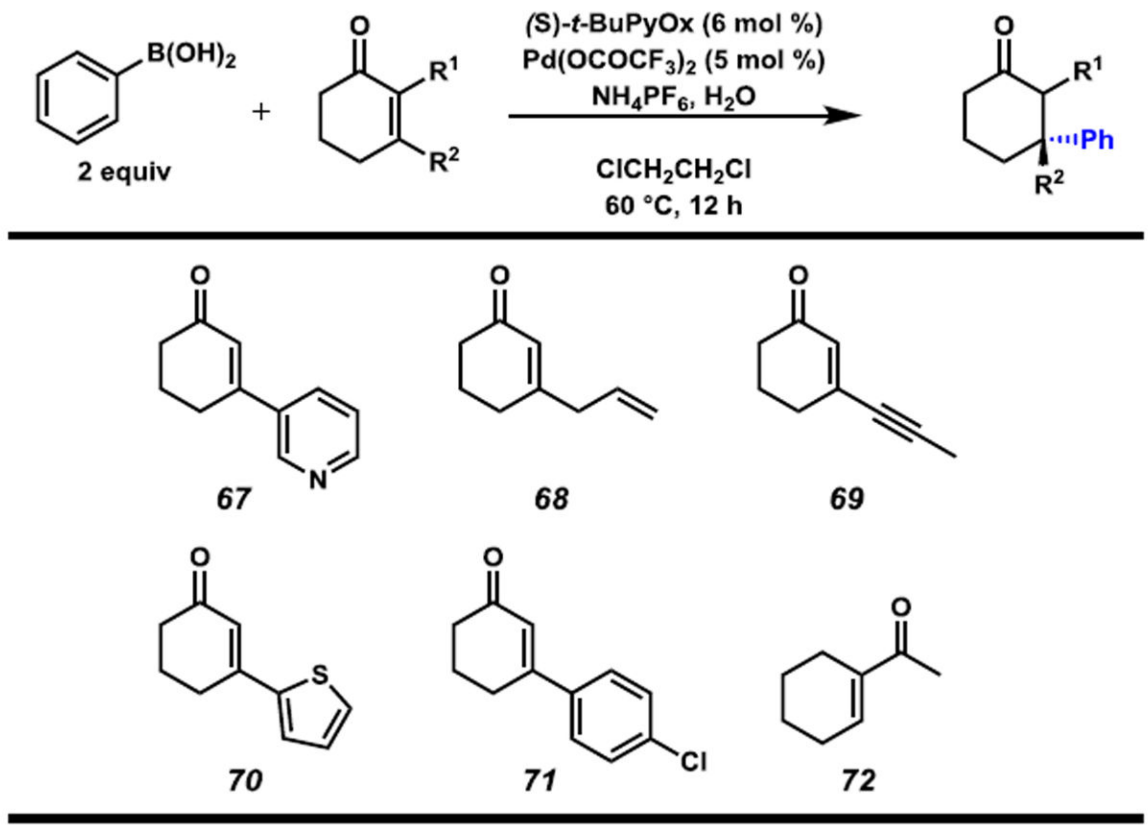
[a]Conditions: Reactions were performed with phenylboronic acid (0.50 mmol), 3-methylcyclohexenone (0.25 mmol), Pd(OCOCF$_3$)$_2$ (5 mol%), and ligand **14** (6 mol%) in ClCH$_2$CH$_2$Cl (1 mL) at 60 °C for 12 h.

[b]Yield of product (**66**).

[c]ee of product (**66**).

Table 12

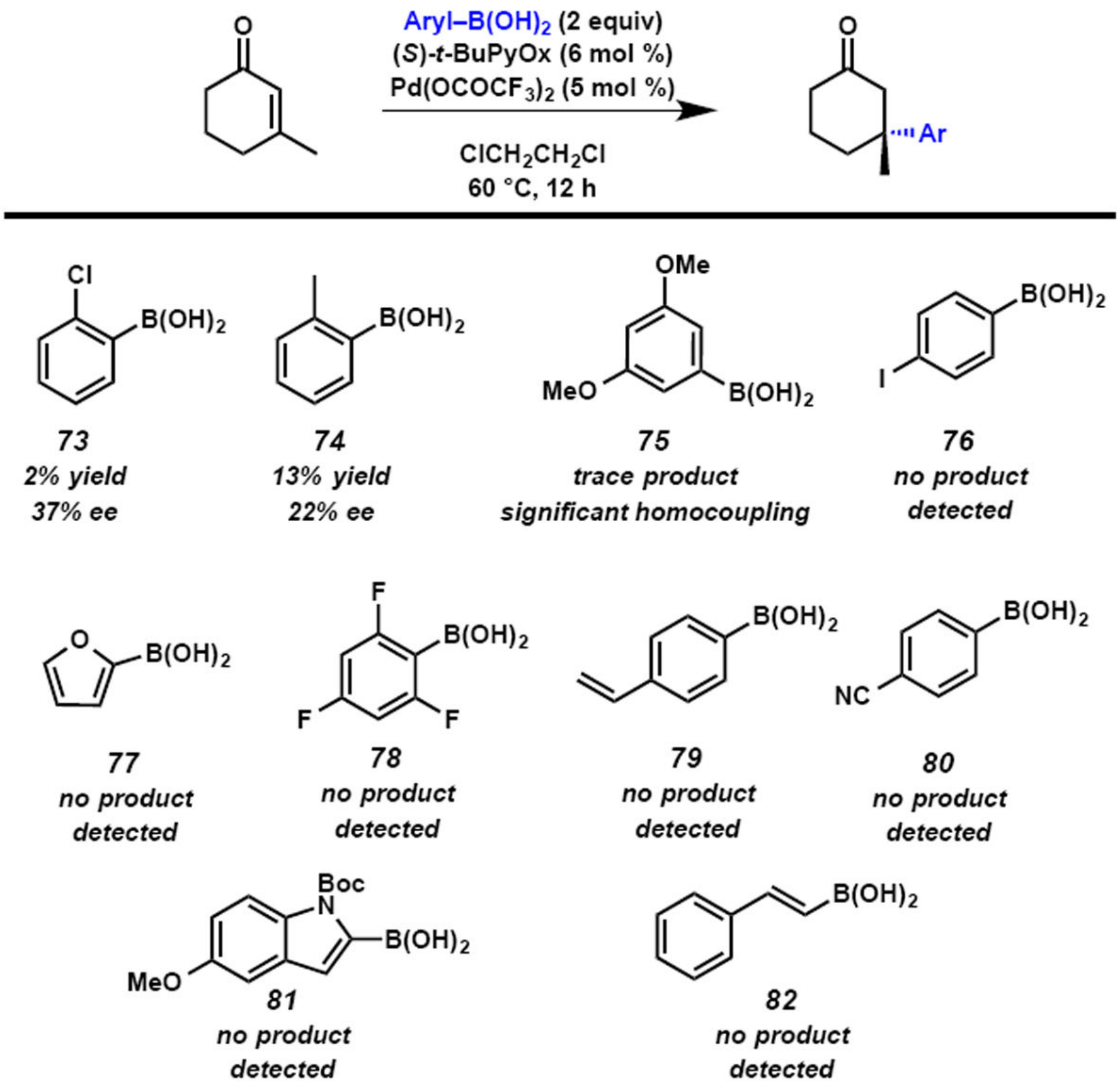
Challenging enone substrates[a]



[a]Optimized reaction conditions afford trace or no conversion as observed by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 13

Challenging boronic acid substrates[a]



[a]Optimized reaction conditions afford trace or no conversion as observed by ^{1}H NMR spectroscopy of the crude reaction mixture.